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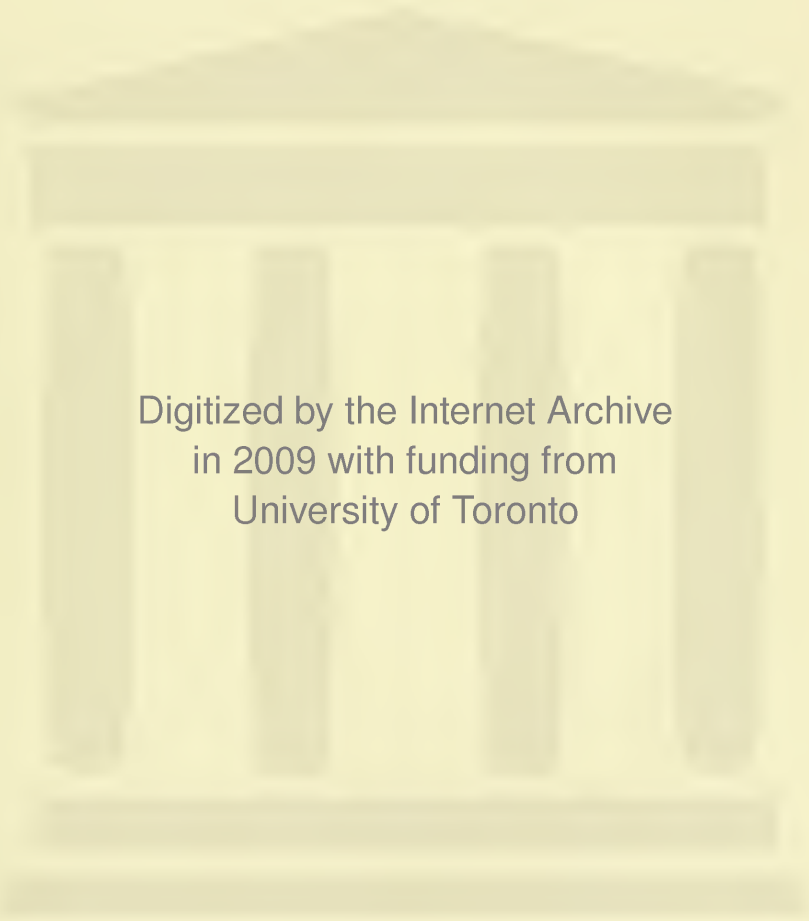
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ORIGINAL ARTICLES

THE OCULAR LESIONS PRODUCED BY DICHLORETHYLSULPHIDE* ("MUSTARD GAS")

By Aldred S. Warthin, Ph.D., M.D., C. V. Weller, M.S., M.D., and G. R. Herrmann, M.S., M.D., Ann Arbor, Mich.

SINCE conjunctival irritation is so prominent a feature of the use in warfare of dichlorethylsulphide ("mustard gas"), the first clinical reports of the effects of this gas emphasized particularly its action on the eyes. These earlier reports speak of the early development (six to twelve hours) of a conjunctivitis in practically all of the men exposed to the gas. The eye-symptoms may appear first, or at the same time with the cutaneous burns. The conjunctivæ are described as congested, the lids very much swollen, with moderate lacrimation, vision not affected in any marked degree, and recovery usually prompt in all the mild cases. These scattered clinical observations are all very superficial, and no thorough studies of the ocular lesions produced by mustard gas are available in the general literature. The best reports are the following, drawn from French and Italian articles.

Giraud (Journal de Médecine et de Chirurgie Pratiques, 1917, lxxxviii, 890), in describing the clinical symptoms of mustard gassing, groups the eye lesions as one of the three cardinal groups of symptoms produced by the gas. He describes these symptoms as essentially congestive. The conjunctival vessels appeared sinuous, dilated, often of a bright red color; and at times in the areas of the finest ramifications of these vessels, at the points of confluence there occur small red "lakes," the size of a lentil. No blisters or ulcerated lesions were noted in the early stages. Pain, as a rule, was quite moderate or absent, although severe in certain cases. Lacrimation was moderate. Impairment of vision was

*From the Pathological Laboratory, University of Michigan, Ann Arbor, Michigan.

exceptional. Pupil reflexes were normal. In some cases the swelling of the eyelids was so marked as to occlude the eye completely. About 10 per cent of the cases seen were characterized by most intense and diffuse congestion. These cases were evacuated. The lighter and moderate cases usually healed in two to three days. Treatment consisted in the use of a solution of soda bicarbonate in strength of thirty parts per thousand.

Teulières (*Journal de Médecine de Bordeaux*, November, 1917, lxxxviii; February, 1918, lxxxix), and *Teulières and Valois* (*Archives D' Ophtalmologie*, 1916-17, xxxv, p. 403) make the first detailed clinical observations on the ocular lesions produced by mustard gas. The great majority of the large number of cases observed presented eye symptoms that were benign and of short duration. Only a small number showed such serious lesions as to make it necessary to send them to a special service for observation. In fifteen hundred cases seen there was but one case of panophthalmitis, and three cases of ulceration of the cornea. In general the symptoms, particularly the photophobia, begin to improve within four to five days, and healing may be complete in two to three weeks. A few cases were seen in which the blepharoconjunctival irritation persisted for a longer time. A detailed description of one of these more severe cases is given. The lids of the right eye, especially the upper, were much swollen and opened with difficulty. Conjunctivæ in the cul-de-sac and in the palpebral portions very hyperemic; on the bulbar portion it was pearly white, porcelain-like, especially in the upper portion, where there was a hard collar of edema. Small punctiform hemorrhages were numerous, and there was a fine deep arborization of the pericorneal vascular plexus. The cornea appeared slightly granular, and no erosion could be demonstrated by the fluorescein method. The iris was congested, but no iritis was present, and no lesions were demonstrable in the interior of the eyeball. Ocular tension normal, ocular movements made difficult by the rigidity of the conjunctiva. Visual acuity, one-tenth. The left eye showed similar changes to a less degree, and without the collar of edema. Vision, ten-tenths. Symptoms were: intense photophobia, continuous lacrimation, smarting and sensation of burning, heaviness of lids, and small amount of yellowish mucopus in the inner angles. Treatment consisted of warm vaporization and the installation of a collyrium of atropine and iodoform ointment. The condition, however, resisted treatment.

In the later paper, *Teulières* and *Valois*, the ocular symptoms are described in fuller detail, as follows: Blepharitis, conjunctivitis, chemosis, edema of lids, congestion of iris, symptoms suggesting a slight iritis, cloudiness of the papilla, slaty tint of the retina (edema?), benign neuroretinitis, congestion of the retinal veins, with diminution of visual acuity. They advance several hypotheses in explanation of the lesions of the posterior segment; (1) that they are secondary to the inflammation of the anterior segment; (2) that the inflammation is an extension through the sinuses and optic meninges, producing a retrobulbar neuritis that may or may not extend as far as the papilla. The lesions of the anterior segment always terminate in healing, and their knowledge of the neuroretinitis cases was too slight to make definite prognosis possible for such cases, although they maintain that both the superficial and deep ocular lesions due to toxic gases are essentially benign. Their treatment consists of warm vapor

baths for the eyes, lasting ten minutes, and repeated four to five times daily; instillations of adrenalin and cocaine for the pain, frequent instillations of atropine for the iris phenomena, and in the cases with neuroretinitis, blood-letting from the temple and mercurial rubs upon the forehead.

Pissarello (*Giornale di Medicine Militaire*, 1918, lxvii, 128) describes the ocular conditions caused by "yprite" (mustard gas). He divides the cases into the light and the moderately grave forms.

The light cases develop five to ten hours after gassing, with headache, burning in eyes, lacrimation, marked photophobia, swollen eyelids, congested conjunctivæ, the bulbar conjunctiva hyperemic in area corresponding to palpebral fissure. Pericorneal infection absent or slight; pupils negative. Symptoms begin to decline in 24-36 hours.

In the severe cases all symptoms more marked, after a shorter incubation period. Eyelids swollen, heavy, "pin prick" pains in eyes; cul-de-sac reddened, chemosis of bulbar conjunction, punctiform conjunctival hemorrhages; cornea usually clean and transparent, in some cases showed desquamation of epithelium. In two cases in which cocaine had been used and a binocular bandage pressed lightly upon the eyes corneal erosions were present. Anterior strata of cornea turbid in some cases due to very minute, grayish white dots. Sometimes this turbidity shows as a grayish white line running horizontally across lower half of cornea. Usually after three to four days there is a remission of the ocular condition. Ulcers, when present, heal rapidly. The pupil formerly contracted dilates readily under atropine. As an exceptional condition cicatricial ectropion was observed. Ophthalmoscopic examination showed in 20 per cent of the graver cases a slight hyperemia of the papilla, with slight tortuosity of the retinal veins. When cases were dismissed there was no disturbance of visual field or visual acuity. He concludes that the ocular lesions are relatively benign. The ocular syndrome reminds him of snow blindness and electric ophthalmia. He believes that the ocular lesions are due to the direct action of the gas and not to any toxic substance in the blood; and conducted a number of experiments, using instillations of tears and sweat from injured soldiers into the conjunctivæ of rabbits, without results. He considers the presence of bulbar chemosis of importance in judging seriousness of cases. As methods of treatment he advises avoidance of bandages and cocaine; and advocates the use of eye wash of 2 per cent bicarbonate or sterile water, with hot vapor fomentations, and a zinc oxide pomade for the lid lesions.

Canelli (*Rivista Ospedaliera*, 1918, viii, 2) describes a fatal case, with autopsy, of poisoning by "yprite" (mustard gas). The eyes presented a diffuse bilateral conjunctivitis, without exophthalmus. No microscopic examination made.

These are the only clinical descriptions available in the general literature; and it is worthy of note that no pathologic studies have as yet been published. In spite of the fact that Victor Meyer, the discoverer of mustard gas noted the conjunctival lesions in man and in experimental animals the literature contains no reports of further investigations in this direction. The material presented by us below must therefore be regarded as opening up a new field in ophthalmic pathology.

Experimental Dichlorethylsulphide Lesions of the Eye

METHOD OF APPLICATION

Application of dichlorethylsulphide to the conjunctiva was made in two ways. In order to secure results comparable to those obtained by direct application to the skin, as previously reported, an extensive series of animals was made use of, in which the liquid dichlorethylsulphide was applied directly to the center of the cornea by means of a fine pipette in uniform minute droplets determined to be about 0.0004 c.c. in size.* The animal's lids were at once released and by its blinking the mustard gas liquid was spread in the conjunctival sac. By using a uniform height of column of dichlorethylsulphide in the pipette the effort to maintain a standard size of droplet was quite successful. However, we realize that slight variations in the amount applied are unavoidable. In another series, the animals were exposed to dichlorethylsulphide vapor in varying concentrations and for varying times in a respiration chamber especially devised for the purpose. Both pure and crude forms of mustard gas were employed.

I. SYMPTOMS AND GROSS PATHOLOGY

Although the objective symptomatology and gross pathology of the lesions produced by direct application of the liquid mustard gas and by exposure to the vapor are essentially similar in the two cases, there are slight differences depending entirely upon method of administration which make it desirable to consider them separately.

DIRECT APPLICATION

The Rabbit.—*At once,* upon application of a standard droplet of dichlorethylsulphide to the center of the cornea, the rabbit blinks repeatedly but shows no other evidence of irritation for one or two minutes when there is usually a period of rapid blinking and rubbing of the eye with the fore paws. At the same time there is a definite increase in lacrimation, but not to the point of epiphora. When at rest the eye may be held partly closed. Thereafter the rabbit shows but slight signs of irritation throughout the earlier stages, except that at long intervals the eye and nose may be rubbed with the paws; the affected eye is not opened as widely as the other and lacrimation is moderately increased. *Fifteen minutes* after application there is beginning congestion of the vessels of the superior palpebral conjunctiva. At the same time there may be a slight decrease in the normal luster of the eye. The fluorescein test is positive as early as ten minutes. (See paragraph below on fluorescein tests.) *Thirty minutes* after application there is increased lacrimation and the congestion of the palpebral conjunctival vessels may now be so marked that there is a pinkish reflex through the upper lid. These changes gradually increase during the next half hour.

At one hour the first evidences of edema appear in the form of localized thickenings of the conjunctiva about 1 mm. in diameter. These occur most

*In our first paper (Journal of Laboratory and Clinical Medicine, May, 1918, vol. iii, No. 8) this was roughly estimated to be 0.002 c.c., but careful weighing has since shown its volume to be as above.

frequently in the superior palpebral conjunctiva near the fornix and at the upper border of the nictitating membrane. These areas are so small and so translucent that they can scarcely be seen except with the aid of the loupe and electric illumination. From *the second to the sixth hour* there is a progressive increase in the conjunctival edema, the localized edematous thickenings extending and coalescing until the ring of swollen edematous conjunctiva so encroaches upon the palpebral fissure that the sclera can not be made visible even by forced separation of the lids. The conjunctiva of the nictitating membrane shares in a marked degree in the formation of this edematous ring. The bulbar conjunctiva also shows a well marked edema, a definite chemosis being noted about the fifth hour. Between the fifth and sixth hours after application the cornea begins to show a faint clouding or haziness, especially in that portion of its lower half exposed in the palpebral fissure. The cornea is less lustrous than normal and when the surface is viewed under oblique illumination it is found to be somewhat roughened and irregular, indicating areas of destruction of the corneal epithelium. There is an increasing formation of seropurulent exudate. Photophobia gradually becomes more marked, the animal resisting all attempts to separate the lids. Lacrimation becomes excessive to the point of epiphora. The pupil reacts promptly to light.

From *the sixth to the twelfth hour* after application the edema of both palpebral and bulbar conjunctivæ continues to increase. There is now a very definite chemosis. At eight hours the clouding of the cornea has reached such a degree that it may be properly described as porcelain-like because of its bluish white opalescence. At this stage, likewise, there was noted an irregularly rounded area devoid of epithelium located in the mesial superior portion of the cornea. At ten hours the lids were found sealed by the accumulated seropurulent exudate along their margins. This adhesion of the lids, first noted at this stage, is a constant feature until the gradual subsidence of the acute inflammatory process about the third week. Very minute subconjunctival hemorrhages are likewise first noted about the tenth hour.

From *the twelfth to the twenty-fourth hour* the picture remains fairly constant. There is a gradual increase in the edema which spreads markedly into the periorbital tissues. (See Figs. 1, 2, and 3.) The stiffened lids stand out widely from the eyeball and along the lid margins there is desquamation of the epithelium and other evidences of necrosis. The corneal opacity is still more marked and in some instances there is a purulent fluid in the anterior chamber. This hypopyon was never in great amount in this stage.

During *the second day* the edema remains so marked that the eye can not be thoroughly examined except by excision. Eyes thus examined at two hour intervals show a continuous progression in the lesion. The edema no longer continues to increase and in the thirty-six-hour specimens a definite decrease can be noted. In spite of this decrease the lids become even more indurated, indicating an increased cellular infiltration, and stand out far from the eyeball. The edges of the lids remain sealed unless forcibly separated and in the pocket thus formed thick purulent exudate accumulates. From the forty-four-hour stage on, this accumulation of thick purulent exudate becomes a very important feature. The denuded area upon the cornea increases in size

and in practically all cases assumes a somewhat circular or elliptical form, occupying the greater part of the corneal surface but always approaching more nearly the inner quadrant of the limbus than the outer. The corneal opacity increases and frequently shows a curious distribution, similar to that which we have since learned has been described in human cases by Pissarello. This consists of a greater degree of opacity in the lower half of the cornea terminating in a more opaque band or zone running horizontally through the cornea

Fig. 1.—Twenty-four hours after direct application of standard droplet of dichlorethylsulphide to cornea of right eye. Marked edema of lids and surrounding subcutaneous tissue.

Fig. 2.—Twenty-four hours after direct application of standard droplet to cornea. Marked edema of lids, flecks of purulent exudate. The marked congestion of the conjunctival vessels is best seen in the bulging edematous mass of the superior palpebral conjunctiva.

Fig. 3.—Twenty-four hours after direct application of standard droplet of crude mustard gas liquid to the cornea. Extreme edema of conjunctiva, especially marked in upper lid and nictitating membrane. Seropurulent exudate.

just below its transverse diameter. This was best seen in a thirty-hour stage. The marginal lid changes become much more marked during this period.

The decrease in the edema continues through the *third* day but is noted especially in the palpebral conjunctiva, while the bulbar conjunctiva, in contrast, exhibits a chemosis which appears even more marked than hitherto.

The necrosis of the palpebral conjunctiva at the lid margins, and even of a zone on the dermal side of the lids becomes more evident, for now there appear numerous shallow ulcerations resulting from separation of the necrotic material.

On *the fourth day* the diminishing edema is followed by an increased congestion. More numerous and larger subconjunctival hemorrhages are frequently noted. These do not, however, occur either in such size or numbers as to permit the lesion to be characterized as hemorrhagic. The lids become increasingly sensitive to pressure so that the animals give evidence of pain when an attempt is made to separate them more widely. In the earlier stages the photophobia seemed to be the feature that gave the animal distress. The upper lid, near the inner canthus, begins to show a "kinking" or "ruffling"

Fig. 4.—One week after direct application of standard droplet to the cornea. Lids still somewhat edematous. They were sealed by a marked purulent exudate which adheres along the lid margins and to the adjacent hair. A marked purulent rhinitis referable to involvement of the mucosa through the nasolacrimal duct, is evident.

of the margin. This is a constant feature in the later stages. The marked seropurulent exudate persists.

There are no marked changes in the lesions during *the fifth day*. The seropurulent exudate is unchanged. The "ruffling" of the upper lid is more marked and the lids are still indurated and stand far out from the eyeball.

In rabbits that have been repeatedly examined, thereby separating the lids and removing the accumulations of purulent and necrotic material, the exudate is less in amount and more serous on *the sixth day*. In animals allowed to remain with the eyelids sealed for days at a time, the seropurulent exudate persists much longer and is, of course, much more destructive. At this time the necrotic lid hairs and the hairs of the face near the inner canthus begin to drop out resulting in some instances in an extensive depilation.

On *the seventh day* there are no marked changes from those previously

described. The depilation about the inner canthus and over the lids is more complete and there is a beginning entropion of the upper lid which has the effect of drawing the stiff outstanding lid somewhat toward the eyeball. (See Fig. 4, a photograph of a rabbit showing the retardation in the course of the lesion when the lids remain sealed and the purulent exudate accumulates in the conjunctival sac.)

Fig. 5.—Two weeks after direct application of standard droplet to the cornea. Marked reduction of the edema. Much less purulent exudate. Indurated lids exhibit the characteristic "ruffling" and partial entropion of the upper lid in the later stages, and the smooth ectropion of the lower lid. The lower half of the cornea shows a marked clouding.

Fig. 6.—Two weeks after direct application of standard droplet to the cornea. Marked depilation about the eye. Characteristic "ruffling" and entropion of upper lid and marked ectropion of the lower. The corneal cloudiness and lack of luster are very apparent, likewise the apparent staphyloma in the lower half of the anterior quadrant.

Fig. 7.—Two weeks after direct application of standard droplet to cornea. Specimen obtained by excision of lids and orbital evisceration. Marked depilation, especially at the inner canthus. Characteristic "ruffling" and entropion of upper lid. Corneal cloudiness.

During *the second week,* the lids of eyes which have been frequently examined no longer become sealed between examinations, and the exudate decreases to a small amount of serous fluid carrying a few flakes of pus and necrotic tissue. The upper lid border comes to show a marked degree of "ruffling" or folding at the lid margin. This is accompanied by an irregularly

distributed entropion. The lid margin itself becomes smooth, rounded and is devoid of lashes. The lower lid shows toward the end of the second week a marked ectropion with the same smooth rounded margin found on the upper lid. The periorbital depilation may be very extensive. The corneal opacity is unchanged. The normal corneal curvature may be distorted by small irregular staphyloma-like projections occurring most constantly inferiorly toward the inner canthus. However, these on section are found to be thickenings of the damaged cornea and not areas of bulging. Hypopyon may be present. (See Figs. 5, 6, 7.)

During *the third and subsequent weeks* the changes in the lesions are slowly progressive, demonstrating the sluggish character of the reparative process following injury with mustard gas. The "ruffling" of the upper lid border persists and gradually becomes more exaggerated up to the eighth week which terminates our period of observation. The ectropion of the lower lid also increases in degree, reaching in some cases an almost complete eversion. The

Fig. 8.—Three weeks after direct application of standard droplet to center of cornea. Same rabbit as Fig. 7. Marked ectropion of lower lid. Porcelain-like cloudiness of the cornea most marked in lower half.

Fig. 9.—Three weeks after direct application of standard droplet of dichlorethylsulphide to cornea. Specimen obtained by excision of lids and evisceration of orbit. Anterior segment of globe in profile to show apparent staphyloma of cornea toward the inner canthus. The cornea cloudiness is well shown.

margins of the lids are rounded, thickened, smooth and glossy, having the appearance of scar tissue. From the fourth week on there is a progressive vascularization of the injured cornea. As the newly formed vessels traverse the limbus the usual sharp differentiation between sclera and cornea becomes effaced. By the sixth week this process of organization becomes far advanced and the new formed vessels may be traced to the central region of the cornea as is clearly shown by Fig. 10. The organization is grossly most evident in that portion of the cornea which showed the primary porcelain-like cloudiness. When this involved the entire cornea, as in the case figured, there results a complete opacity of the cornea, so that the iris and pupil can no longer be seen and blindness must be nearly, if not quite, complete. (See Figs. 8, 9, 10, 11, 12.)

The Dog.—Following the direct application of a standard droplet of liquid dichlorethylsulphide to the cornea of the dog, the changes run closely parallel to those described above for the rabbit and it seems unnecessary to describe

them in detail. The earliest changes are identical. At the period, however, at which the rabbit's eye becomes sealed by the adhesion of the lid margins, the powerful orbicularis muscle of the dog prevents this occurrence. As a result there is never the empyema of the conjunctival sac that is found in the rabbit and the exudate seems to be less in amount. The congestion in the

Fig. 10.—Six weeks after direct application of standard droplet to cornea. Combined ectropion and entropion of upper lid with resulting "ruffing" of lid margin. Ectropion of lower lid. Organization of the necrotic cornea with extensive arborizations of newly formed blood vessels, best seen in the upper half of the cornea. Even in the photograph these can be traced from the sclera across the superior arc of the limbus to the central portion of the cornea. The same eye is shown in the next two figures, taken one week later and after excision.

Fig. 11.—Seven weeks after direct application of standard droplet to cornea. Excised specimen. Complete opacity of cornea with vascularization. "Ruffling" of upper lid with areas of entropion and very marked smooth ectropion of lower lid. Apparent irregular staphylomata of cornea are areas of thickening due to infiltration and organization.

Fig. 12.—Seven weeks after direct application of standard droplet to cornea. Same eye as in preceding figure. Here shown in profile to show marked irregularity of corneal surface. Note especially the prominent apparent staphyloma in the sclera toward the inner canthus.

earlier stages is more marked, or at least more evident, than in the rabbit. The edema and the corneal necrosis are similar with the exception that the localization of the corneal opacity in the lower segment was never noted.

EXPOSURE TO MUSTARD GAS VAPOR

THE RABBIT.—The symptoms and gross pathology produced by exposure to mustard gas vapor vary with the concentration of the vapor and the length of exposure. In any case, they differ in degree, but not in kind, from those produced by the direct application of the liquid dichlorethylsulphide to the cornea and its immediate spread throughout the conjunctival sac by blinking. An exposure for fifteen minutes to a concentration of approximately 1:20,000 was found to give results of about the same degree of severity as those produced by the standard droplet of liquid directly applied. The following notes are abstracted from a protocol of a rabbit subjected to mustard gas vapor for that time and at that strength.

About five minutes after being placed in the gassing chamber the animal commenced to show signs of irritation, increased blinking, rubbing of the eyes and nose, and a change of position to bring the head as far as possible from the affluent opening by which the impregnated air was being introduced. Immediately after removal from the chamber the animal was quiet but after a short interval continued to show increasing signs of irritation of the conjunctival and respiratory mucosa. These continued for the next few hours. At five hours after gassing a well-marked conjunctivitis was present. There was increased lacrimation, redness of the lid borders, beginning edema and a marked photophobia. After sixteen hours the signs and symptoms were all much more marked. The exudate had become somewhat mucopurulent; congestion of the lid borders and conjunctiva was increased and likewise the edema. The animal kept both eyes closed because of the photophobia, which seemed much more marked. The edema reached its height about twenty-four hours after exposure, and a well marked chemosis was then evident. All skin surfaces where the hair was thin showed a definite erythema. This was especially marked on the lids and convexity of the ears. A bilateral rhinitis with abundant serous exudate also appeared at this time. The inflammatory changes of the upper respiratory tract were much worse at thirty-six hours, the wheezing respiration being distinctly audible at a distance. The eyes were sealed, and upon separation of the lids a large amount of thick purulent exudate appeared. The conjunctivæ were edematous and congested, and there were a few minute subconjunctival hemorrhages.

The lesions progressed slowly as described for those produced by direct application. At seventy-two hours the clouding of the lower half of the cornea had appeared to a marked extent. The lids, having lost their edema to a considerable degree, remained stiff and stood out far from the eyeball, showing the first signs of the "ruffling" previously described. At ninety-six hours the lid borders began to show loss of the necrotic epithelium with the formation of shallow ulcers. The corneal surface became roughened through loss of the epithelium, but no deeper ulceration could be demonstrated.

The lesions produced by this method have not been observed up to the stage of complete healing, as was done with those produced by direct application; but there are no apparent differences in the nature of the sluggish reparative processes in the two cases.

SUBCUTANEOUS INJECTION AND INGESTION OF DICHLORETHYLSULPHIDE IN RELATION TO OCULAR LESIONS

We have attempted to verify the statement of Victor Meyer that subcutaneous injection of dichlorethylsulphide determines the occurrence of a conjunctivitis, indicating not only a metastasis of the toxic substance through the blood stream, but also a selective affinity or special susceptibility of the conjunctiva. For this purpose we have used a series of four albino rabbits, two hares and two dogs. The albino rabbits offered the greatest prospect of success, since in them the slightest conjunctival congestion can be readily seen. In the cases of the rabbits and hares one minim of dichlorethylsulphide was given as a subcutaneous injection. In no instance was any trace of conjunctivitis or any other ocular change produced. The site of injection developed a wafer-like induration which dried down to a deep-seated eschar. In every case there developed a foul diarrhea to which most of the animals succumbed on about the sixth day. One large dog received four minims subcutaneously. There was no conjunctivitis, but a severe diarrhea developed, and death occurred on the fourth day. Another dog was fed 4 minims in meat. Severe burns of the mouth and upper alimentary tract were produced but there was no conjunctivitis. These lesions in the gastrointestinal tract will be considered more fully in a subsequent report. Attempts to produce conjunctivitis or other eye lesions by intravenous injection have also failed; although this fact has little weight since death occurs too soon to permit the development of marked changes.

RELATIONS OF PANOPHTHALMITIS TO DICHLORETHYLSULPHIDE LESIONS

In the ocular lesions produced by the standard droplet and by exposure to a vapor concentration of 1:20,000 for fifteen minutes, with ordinary care given to the eyes so treated, by separation of the lids to allow the purulent exudate to drain out, no evidence of panophthalmitis was observed; and by the end of the fourth week healing was usually complete. But in animals exposed as above, with eyes untreated, lids allowed to remain sealed and exudate to accumulate, within three weeks there may develop a purulent panophthalmitis which by the sixth week usually destroys the entire eyeball with complete suppuration of all orbital tissues. When a larger dosage is given, and the eyes untreated, a panophthalmitis may develop more rapidly. (See Fig. 43.)

Protocol.—One series of four rabbits was treated with a heavy application of liquid dichlorethylsulphide to the center of the cornea. The amount applied was about twice that of the standard application. In three rabbits the eyes were left untouched for five weeks, in the fourth for six weeks. After the first sealing of the lids there was no separation of the same to allow the purulent exudate to escape. As a result an empyema of the conjunctival sac developed with subsequent destruction of the eye from a suppurative panophthalmitis. These eyes all showed the same gross picture; perforation of the cornea, necrosis and abscess formation, loss of the contents of the globe, and suppuration of all orbital contents.

In our cases the occurrence of panophthalmitis is due entirely to secondary infection, which occurs ultimately after several weeks in the untreated cases after slight gassing; but much more rapidly after heavier dosage. The pathologic changes produced by dichlorethylsulphide are covered up by those due to secondary infection.

FLUORESCEIN TEST

The standard method of applying an alkaline aqueous solution of fluorescein for the determination of corneal ulceration was carried out on a series of eyes at different time intervals following exposures to dichlorethyl-sulphide. A 2 per cent alkaline watery solution was used. Ten minutes after the direct application of the standard droplet to the center of the cornea, several minute pinpoint areas at the vertex of the cornea retained the fluorescent green coloration. These minute areas increased in number so that, within fifteen minutes after the exposure, the vertex of the cornea appears peppered with these spots in a small circular area. These pinpoint areas increased in size, and became confluent in about thirty minutes after exposure. By one hour they were fairly uniformly confluent. From this time on the fluorescein staining showed a gradually increasing depth of penetration and a spreading of the circumference of the staining area over the cornea, especially toward the inner canthus. The depth of the intravital staining reaction is greatest at the vertex of the cornea and decreases laterally. At the end of forty-eight hours a narrow crescentic area toward the outer canthus remains unstained showing that the necrosis in this area occurs more slowly than elsewhere. After exposure to the vapor of dichlorethylsulphide the fluorescein staining reactions are the same as after direct application. This intravital fluorescein staining is parallel in intensity to the necrosis of the corneal epithelium as shown by the microscopic study of the same stages. The earliest intravital staining occurs at the same time that the pyknosis of the corneal epithelium becomes evident, before any ulceration or abrasion takes place. The use of this test is therefore of the greatest importance clinically in determining the severity and progress of the lesions and the effects of therapy.

SUMMARY OF GROSS PATHOLOGIC CHANGES

1. The standard drop of 0.0004 c.c. when applied directly to the cornea of animals was found to produce results practically identical with those produced by an exposure of 15 minutes to a vapor concentration of 1:20,000. The criticism, therefore, that the use of the standard drop produces changes not comparable to those observed in exposure to dichlorethylsulphide vapor does not hold. Further, the use of the standard drop is a much more convenient and accurate way, as well as a safer method, of handling this material for experimental purposes. Further the use of the direct application method avoids the complication of respiratory or general cutaneous involvement following the exposure of the animal in a gas chamber.

2. Dichlorethylsulphide produces after one or two minutes exposure to drop or highly concentrated vapor a definite irritation of the conjunctiva with

increase of lacrimation. Usually within thirty minutes there is a well-marked hyperemia, followed in an hour by the development of edema, which progresses rapidly up to the twelfth hour when there is usually a well-marked chemosis. Minute subconjunctival hemorrhages may develop as early as the tenth hour.

3. In animals the edema develops first and most markedly in the palpebral conjunctiva, following the direct application, while in the exposure to mustard gas vapor it frequently develops first in the bulbar conjunctiva, this being practically the only difference observed in the effects of the two methods. By the end of the third day the edema begins to subside slightly, but persists to some degree for several weeks. In man the edema is less marked, more irregular, while the hyperemia is more marked, and minute vesicles may be found on the conjunctival surface.

4. The necrosis of the cornea is shown by a definite cloudiness developing in five to six hours which usually at eight hours has reached such a degree that the cornea takes on a porcelain-like appearance in the form of a very characteristic bluish white opalescence. In the mildest cases the lesion does not progress beyond a slight cloudiness. Intravital staining with an alkaline aqueous solution of fluorescein shows very early the development of the corneal necrosis, even before ulceration has occurred. A striking phenomenon is the frequent occurrence of a more opaque band or line running horizontally across the cornea just below its transverse diameter.

5. A seropurulent exudate is well developed by the fifth to the sixth hour and increases until the eyelids are usually sealed by the accumulated exudate by the tenth hour. This adhesion of the lids remains a constant feature until the gradual subsidence of the inflammatory process about the third week. The edges of the lids remain sealed unless forcibly separated. If the eyes are frequently examined with consequent separation of the lids and removal of the accumulated exudate, the stage of purulent exudation is preceptibly shortened.

6. With the subsidence of the edema a characteristic kinking or "ruffling" of the upper lid, a combined entropion and ectropion, appears, usually by the fifth or sixth day. At the same time the lower lid begins to exhibit a smooth ectropion.

7. Depilation of the lid hairs and of the face hairs, eventually about the entire orbit, takes place.

8. During the second week changes in the corneal curvature are constantly noted, some of these so marked as to appear staphyloma-like.

9. Hypopyon sometimes occurs. Clouding of the contents of the anterior chamber occurs quite regularly in the later stages.

10. From the third week on the lesions slowly progress in a manner characteristic of the mustard gas lesion of the skin towards resolution and repair. The "ruffling" of the upper lid increases up to the eighth week while the ectropion of the lower lid frequently reaches the point of complete eversion. Progressive vascularization of the cornea takes place, the vessels usually reaching the center of the vertex by the end of the sixth week. Corneal cicatrization, marked impairment of vision, and thickening of the eyelids and nictitating membrane are the ultimate sequelæ. Even in the lighter cases in man,

the edema and hyperemia of the conjunctivæ tend to run a chronic course with resulting visual disturbances and reduction of vision. An increased susceptibility to the vapor may develop.

11. Secondary infection. In animals exposed to the standard drop or vapor concentrations of 1:20,000, followed by treatment of the eyes, purulent panophthalmitis has not been observed to develop. In the case, however, of untreated eyes, and following heavier dosage, suppurative panophthalmitis does develop with complete destruction of the eyeball.

II. MICROSCOPIC PATHOLOGY

Technic.—Every care was taken to prevent the formation of artefacts, either postmortem or technical. The eye was removed at once from the freshly killed animal by a wide incision encircling the lids and eviscerating the orbit. It was at once placed in the fixing fluids, a neutral formol being used for the greater part. The specimen was left in the fixing fluid about forty-eight hours before being sectioned, at which time uniform blocks of tissue were selected. These were so oriented as to give vertical sections through the entire eyeball, a section through the inner canthus and one through the lacrimal gland from each eye. The lens was removed from the eyeball after thorough hardening, in order to facilitate the cutting of thin sections. These tissues were embedded in paraffin, the sections were transferred to the celloidin sheet and stained with hemalum and eosin and by other ordinary staining methods.

Rabbit.—*One Quarter Hour.*—The changes observed are of slight degree, consisting of contraction and pyknosis of the corneal epithelium which is more marked at the vertex and less marked over the limbus. Likewise the cells of the substantia propria show a slightly greater degree of pyknosis and contraction than in control preparations. The bulbar and palpebral conjunctivæ show a similar pyknosis and contraction. In the fornix there is a more decided vacuolation of the conjunctival epithelium. The epithelium of the cutaneous surface of the eyelid shows also slight pyknosis and contraction. In the region of the inferior fornix alone does the subconjunctival connective tissue show a well-marked edema. In the upper fornix the edema is less marked. The lacrimal gland shows a marked distention of its gland spaces which are filled with secretion. Harder's gland and the tarsal glands show no changes, likewise the sinus hairs. The blood vessels of all parts are anemic rather than congested. There is no hemorrhage and no thrombosis.

One Half Hour.—Changes identical with those above, except a little more marked in degree. Pyknosis and vacuolation are a little more pronounced. The edema is much greater, particularly around the lacrimal gland. The distention of the lacrimal gland is greater, and its cells show a marked vacuolation. Greater congestion in all parts.

One Hour.—The only changes are an increase in the edema and congestion.

One and One Half Hours.—The pyknosis of the corneal epithelium is as above, but the substantia propria shows a distinctly more marked pyknosis of the corneal cells extending entirely through the cornea at the vertex. A large

portion of the endothelium of the anterior chamber shows marked pyknosis and contraction. The conjunctival epithelium, both bulbar and palpebral, shows an increased degree of pyknosis while the subconjunctival connective tissue shows now a marked edema, extending entirely through the eyelids. It is especially noteworthy that many of the blood vessels appear partly collapsed, with a relative anemia, while others are moderately congested. The lacrimal gland shows the same active secretion, many of the acini being greatly dilated, and filled with secretion. The vessels of the gland are congested and there is an increased number of wandering cells throughout the gland. The stroma of the gland and the surrounding stroma show extreme edema. The tarsal glands show groups of pyknotic alveoli. The epithelium of the membrana nictitans shows less change than that of the bulbar and palpebral conjunctivæ.

Two Hours.—(See Fig. 13.) Pyknosis of the corneal epithelium is complete. It is impossible to recognize the individual cells. The substantia propria stains more diffusely blue and the endothelium of the anterior chamber shows a greater degree of pyknosis and vacuolation. Similar changes occur in the

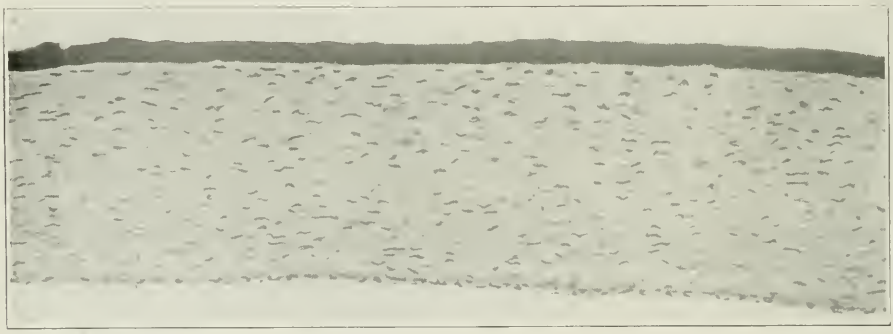

Fig. 13.—Cornea two hours after application of standard droplet. First stage of necrosis of corneal epithelium and of the cells of the interstitial substance. Marked pyknosis of the corneal epithelium, the cells of the lowest layer alone being barely distinguishable. The nuclei of the interstitial substance and of the endothelial lining of the anterior chamber are also pyknotic. Section taken at corneal vertex.

palpebral and bulbar conjunctivæ and in the epidermis of the eyelids. The edema of the eyelids is now extreme, being most marked on the conjunctival surface. (See Fig. 27.) There is an increase of wandering cells throughout both upper and lower eyelids, but no well-marked cellular infiltrations. Many of the blood vessels show a well-marked congestion. The membrana nictitans shows a marked pyknosis of its epithelium and a marked edema of its stroma, its thickness being increased about ten fold. The lacrimal gland shows a marked distention of all its gland spaces and a marked vacuolation of its epithelium which appears distinctly more columnar in shape. The cells of Harder's gland stain very deeply and are contracted and pyknotic, and have lost their granular appearance to a marked degree. The Meibomian glands show a similar marked pyknosis involving all of the alveoli. The adipose tissue around the eye and about the tarsal glands shows a marked edema and gives a marked mucin staining reaction.

Three Hours.—The cornea is as before. The epithelium of the conjunctiva, both bulbar and palpebral, shows a greater degree of necrosis. The edema is

much more marked beneath both the bulbar and palpebral conjunctiva, amounting almost to a liquefaction of the tissue. There is now a well marked polynuclear infiltration beneath the conjunctival epithelium and extending throughout the entire lid. The epidermal surface of the eyelids shows now a well-marked pyknosis and karyorrhexis of the nuclei of the dermis, particularly of of the papillary layer, with a well-marked polynuclear infiltration, the changes being identical with those described in the article on the skin lesions, with the exception that the cellular infiltration is somewhat more prominent than was found in the skin. The vessels show a more marked congestion than in any of the previous stages. The lacrimal gland shows the same distention of the alveoli but the cells are less columnar and the nuclei show some pyknosis and karyorrhexis. The gland of Harder and the tarsal glands show the same pyknosis as in the preceding stage. The changes in the epidermal surface of the eyelid have advanced in necrosis and cellular infiltration.

Four Hours.—Changes in the cornea appear as in the preceding. Bulbar

Fig. 14.—Section of cornea at vertex five hours after direct application of standard droplet. Desquamation of necrotic epithelium in center of vertex. Pyknosis of remaining epithelium and of cells of the interstitial substances. Complete necrosis of endothelial cells of anterior chamber.

and palpebral conjunctivæ, membrana nictitans and epidermal surface of eyelids show increasing edema and cellular infiltration. The lacrimal gland shows extreme distention and the cells of many acini are flattened and vacuolated as in a state of exhaustion atrophy. Harder's gland shows a well-marked vacuolation of its epithelium, many of the cells showing large clear droplets, edema. Likewise the tarsal glands show edema. In the palpebral and bulbar conjunctivæ the cellular infiltration is increased, and the lymph follicles in the palpebral conjunctiva show great numbers of wandering cells. Vessels are greatly congested.

Five Hours.—(See Fig. 14.) The corneal epithelium is in part desquamated over the region of the vertex, and about this the epithelium shows marked dissociation and vacuolation. The substantia propria now stains lighter in color, many of its nuclei being only shadows. At the sclerocorneal junction there is

now a well-marked infiltration of polynuclears, most marked just beneath the pyknotic epithelium. The upper and lower lids show extreme edema (see Fig. 28) and marked small-celled infiltration extending through the entire thickness and there is a marked infiltration of polynuclears throughout, which is more marked beneath the palpebral conjunctiva near the palpebral border. In this region the conjunctival epithelium is desquamating and there is developing an ulcerating surface. The adherent dead epithelium is infiltrated with polynuclears. The blood vessels show congestion. There is no thrombosis. On the epidermal border of the lids there is beginning desquamation of the dead epidermis. The sebaceous glands near the margin of the lid show sebum retention. Likewise on the lower lid near the palpebral margin, there is noted the first development of ulcer or slough, and the membrana nictitans shows loss of its epithelium in areas. Lacrimal, Harder's and tarsal glands, as in the preceding.

Six Hours.—Changes identical with above.

Eight Hours.—The only change noted from the above is an increase in the ulcer on the conjunctival surface near the palpebral margin in both upper and lower lids, more marked in the upper. (See Fig. 29.)

Ten Hours.—Cornea shows gradual loss of chromatin. Stains more palely. On the eyelids the necrosis of the epidermis and eschar formation has progressed while almost the entire conjunctival epithelium is completely disintegrated, forming a granular layer infiltrated with polynuclears. The exudate is most marked near the palpebral border where there is a distinct ulcer covered with exudate. Intense edema and congestion as in the preceding. Small pinpoint hemorrhages occur in the subconjunctival connective tissue. Both the lacrimal and Harder's glands show more marked vacuolation. Increased polynuclear infiltration throughout, extending even into the orbital tissues.

Twelve Hours.—At the corneal vertex the cornea is dead throughout having completely lost its nuclei. The corneal epithelium is desquamated over the vertex, and only here and there are there faint outlines of the nuclei of the substantia propria. The pyknotic and vacuolated endothelium of the anterior chamber is still intact. The escharization of the epidermal surface of the lids is complete, and desquamation of both bulbar and palpebral conjunctival epithelium is nearly complete. Congestion is very marked and there are numerous minute hemorrhages by diapedesis both beneath the epidermal surface and in the subconjunctival connective tissue. The edema is even more marked than in the preceding stages, involving the whole eyelid, and the lymphatics are enormously distended. The lacrimal gland is as before, but Harder's and the tarsal glands show marked edema and liquefaction necrosis. There are masses of exudate, rich in polynuclears, adherent to the conjunctiva at the lid margins, the result of drying and concentration of the secretion, but near this, minute collections of polynuclears beneath the conjunctiva suggest beginning infection. The fluid of the edema now assumes the same hyaline, finely granular, deeply pink staining appearance as found in the subcutaneous tissues. (See Article on Skin Lesions.*)

Fourteen Hours.—Changes as above, but slightly advanced. Intense con-

*Journal of Laboratory and Clinical Medicine, May, 1918, iii, No. 8.

gestion. Polynuclear infiltration of the muscle. Numerous hemorrhages about the greatly distended vessels. Secondary thrombosis beginning. More marked polynuclear infiltration into the subconjunctival connective tissue. Heavy granular precipitate in the distended alveoli of the lacrimal gland. These contain, likewise, great numbers of albuminous spherules, staining deep violet or pink, derived from the disintegration of the cells.

Fifteen Hours.—Changes as above with more marked polynuclear infiltration at the sclerocorneal junction, in the ocular muscles and in the orbital tissues. Beginning infection of the conjunctival ulcers near the palpebral border. Diffuse inflammation of the entire peribulbar tissues. It is a notable fact that the sebaceous glands on the epidermal surface of the lids show penetration with the dichlorethylsulphide, and necrosis while the large ones at the palpebral margin seem to escape.

Sixteen Hours.—Complete loss of the necrotic epithelium over the corneal vertex. Increasing polynuclear infiltration at the sclerocorneal junction. Edema of the ciliary body and ciliary ring. Increasing polynuclear infiltration and greater collection of pus at the palpebral borders.

Eighteen Hours.—Nearly complete necrosis of the cornea except toward the periphery of the limbus. On the lids escharization is extending, the necrosis reaching into the subconjunctival tissue and into the subepidermal tissues on the cutaneous side. It is notable, however, that the subcutaneous necrosis is deeper than the subconjunctival. On the skin surface the necrosis extends nearly through the depth of the lower border of the sebaceous glands. The epithelium of the entire margin of the lids is now completely necrosed and desquamated. Over the entire surface of the conjunctiva including the membrana nictitans the epithelium is now necrotic and desquamating, but the necrosis extends but very little into the subepithelial connective tissues. For the first time changes are observed in the erectile sinus hairs of the upper lid, the epithelium of the hair follicle showing some pyknosis and contraction.

Twenty Hours.—Complete necrosis of the cornea, in the central portion extending to the endothelial lining of the anterior chamber which is partly necrotic and desquamating. Conjunctival, lid and gland changes as above. The large sebaceous glands at the lid margin show a more marked polynuclear infiltration than in any of the preceding. Congestion, edema and minute hemorrhages as in preceding stages.

Twenty-two Hours.—Complete death of cornea in central portion, with loss of epithelium and endothelium of anterior chamber. Only scattered nuclei through the dead substantia propria. Eyelids show the same extreme edema, congestion and numerous hemorrhages by diapedesis around the congested vessels as in the preceding, but with an increasing small-celled infiltration. Fibroblastic proliferation first observed in the subconjunctival connective tissue.

Twenty-four Hours.—Cornea completely necrotic except near the sclerocorneal junction. Its laminæ are separated and there is a collection of fluid between the separated laminæ. Edema at its height; other changes as above.

Twenty-six Hours.—Necrosis of the cornea complete with marked separation of the laminæ into irregular spaces. Edema as in preceding, but poly-

nuclear infiltration much more marked extending throughout the entire thickness of the lids. Marked distention of the acini and atrophy of the cells of the lacrimal gland. Numerous capillary hemorrhages by diapedesis throughout the subconjunctival tissues and the dermis of the lids. (See Fig. 31.)

Twenty-eight Hours.—As in the preceding, no difference.

Thirty Hours.—(See Fig. 15.) Identical with the preceding stages.

Thirty-two Hours.—Most marked changes in the cornea, particularly at the vertex. Surface roughened, nobby, laminæ separated. Changes in lids and glands as in preceding.

Thirty-four Hours.—The central portion of the cornea shows complete necrosis but at the periphery there is a marked cellular infiltration and proliferation of corneal cells. At the sclerocorneal junction there is an evident fibroblastic proliferation. The edema of the upper palpebral conjunctiva is less marked; cellular infiltration about as before, but more cells of a fibroblastic type. The edema of the lower lid is the most marked yet seen, a large portion

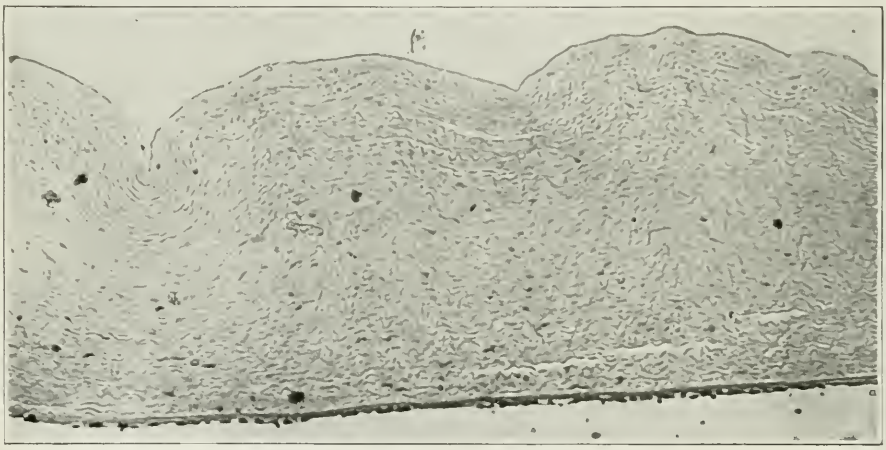

Fig. 15.—Cornea thirty hours after exposure to vapor of dichlorethylsulphide. Complete necrosis of cornea.

of the subconjunctival connective tissue showing complete liquefaction necrosis with marked polynuclear infiltration. (See Figs. 32, 33.) The cutaneous border of the lower lid shows a marked depilation, almost every hair having been shed. The upper lid shows a less marked depilation. The lacrimal gland shows in various areas a very marked hypertrophy of the cells. These are more columnar with a very deeply staining protoplasm. Other portions show the light vacuolated cells as described above.

Thirty-six Hours.—Changes as in the preceding, except for the membrana nictitans which shows marked congestion of its vessels and multiple capillary hemorrhages. The ocular muscles show marked edema.

Thirty-eight Hours.—The most marked necrosis of the cornea, the complete necrosis extending almost to the sclerocorneal junction. Complete necrosis of the endothelial lining of the anterior chamber with increased number of leucocytes in the fluid of the anterior chamber. On the lids there is beginning regeneration of the epidermis and hair follicles, but no evidences of regenera-

tion of the conjunctiva. Almost complete depilation. Edema persistent in the subconjunctival tissues, and at the palpebral margins there is a marked collection of pus.

Forty Hours.—Necrosis of cornea less marked than in preceding individual; endothelial lining preserved. Appearances indicate a somewhat earlier stage, probably due to less intense action.

Forty-two Hours.—(See Fig. 16.) Marked necrosis of the central portion of the cornea. The membrane of Descemet and the endothelium of the anterior chamber appearing as a hyaline red line bordering the anterior chamber. Proliferation of corneal cells at border of cornea; fibroblastic proliferation at sclerocorneal junction. Beginning separation of eschar on epidermal side of lids and also on the conjunctiva. Cutaneous lesion much deeper and more severe than the conjunctival, although the oedema is much more marked on the conjunctival side, as is also the leucocytic infiltration.

Forty-four Hours.—Changes the same as at forty-two hours but of less

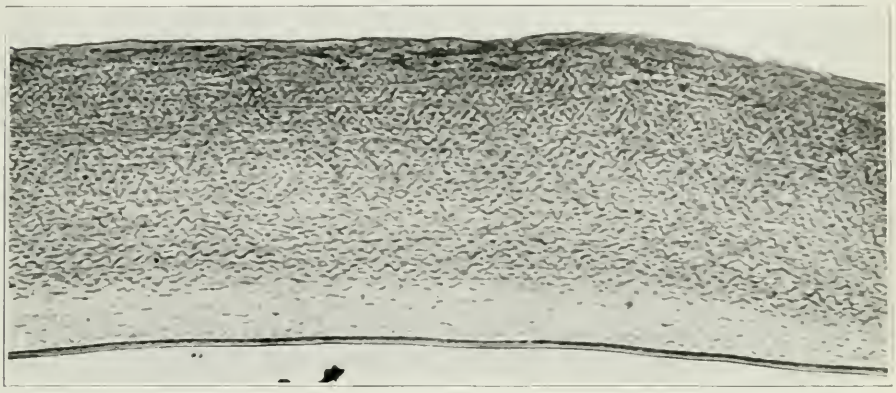

Fig. 16.—Cornea forty-two hours after application of standard droplet. Membrane of Descemet appears as a bright hyaline line staining red with eosin.

intensity. Probably due to dilution of dose on the cornea. The skin surface of the lids shows marked escharization.

Forty-six Hours.—No essential differences.

Forty-eight Hours.—Corneal changes same as in the preceding. More marked escharization of the lids and conjunctival surfaces. Beginning separation of the eschar on epidermal portion of lids. Almost complete depilation.

Fifty Hours.—Very marked separation of corneal lamellæ and formation of irregular spaces. Partial separation of the slough on the cutaneous surface of the eyelids. Well-marked regeneration of the hair follicles. Old hairs nearly entirely shed. The membrana nictitans is markedly hemorrhagic. The large sinus hairs show marked necrosis of the epithelium of the hair follicle. Very marked fibroblastic proliferation in upper lid.

Fifty-four Hours.—Changes as in preceding, except for more marked escharization of the epidermal surface of lids, and more marked fibroblastic proliferation of the subcutaneous tissue. Marked congestion and numerous hemorrhages, particularly on the epidermal side of the lids.

Sixty Hours.—Shrinking and drying of the cornea at its vertex. Fibroblastic proliferation on the dermal side of the lids very marked. Epithelial regeneration well advanced. Beginning regeneration of conjunctival epithelium, but the greater part of the conjunctiva remains denuded. The lower lid shows many hemorrhages throughout its substance; the hemorrhages are more marked than in any other case. The eschar on the dermal side has completely separated with regeneration of the epidermis and hair follicles. Very few of the old hairs are left. Edema is still persistent on the conjunctival side, but less marked.

Sixty-five Hours.—Cornea shows regeneration of the corneal cells throughout its entire extent, but most marked at the periphery. There is marked regeneration of the endothelium of the anterior chamber with plasmodial masses of epithelium on the surface. Anterior chamber contains large numbers of leucocytes. Lids show marked edema, extreme congestion and multiple hem-

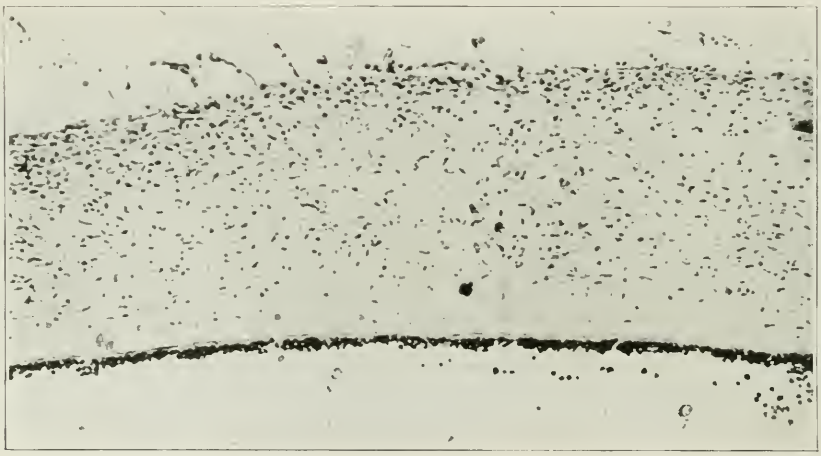

Fig. 17.—Cornea three and one-half days after application of standard droplet. Complete necrosis of corneal tissue; ulceration of surface; beginning infiltration with polynuclear leucocytes and collection of polynuclear leucocytes along the line of the necrotic endothelium.

orrhages. Eschar on epidermal side is very deep and not completely separated. Changes much more severe than in the preceding instance with less regeneration and repair.

Seventy-two Hours.—Edema of lids still very marked. Deep escharization on epidermal side with eschar separating. Very little regeneration and repair. In the lower lid the edema is very marked, with liquefaction necrosis of the subconjunctival connective tissues.

Eighty-four Hours.—(See Figs. 17, 18.) Complete necrosis of cornea with no evidence of repair except at the limbus. Very marked congestion and numerous hemorrhages in the lids. Nearly complete depilation with regeneration of epidermis and hair follicles. Membrana nictitans markedly hemorrhagic and shows some fibroblastic proliferation.

Ninety-six Hours.—Cornea completely necrosed in the vertex. Proliferation of corneal cells toward the limbus. Fibroblastic proliferation near

sclerocorneal junction. Very deep escharization of epidermal side of lids with separation of eschar. (See Figs. 34, 35.) Regeneration of conjunctival epithelium in various portions of both upper and lower lids. Edema of lids much less marked, but lids are thickened by the marked fibroblastic proliferation.

One Hundred Ten Hours. Cornea completely necrosed in central portion. At limbus it shows polynuclear infiltration and fibroblastic proliferation. Anterior chamber contains numerous polynuclears, pus. Iris and ciliary body show cellular infiltration. Conjunctiva shows areas of regeneration of epithelium. Edema is less marked. The gland of Harder shows liquefaction necrosis, as do also the tarsal glands. Necrosis of the epidermal side is deep, but the eschar has nearly completely separated and there is regeneration of the epithelium in some areas and of the hair follicles. Edema of lids is much

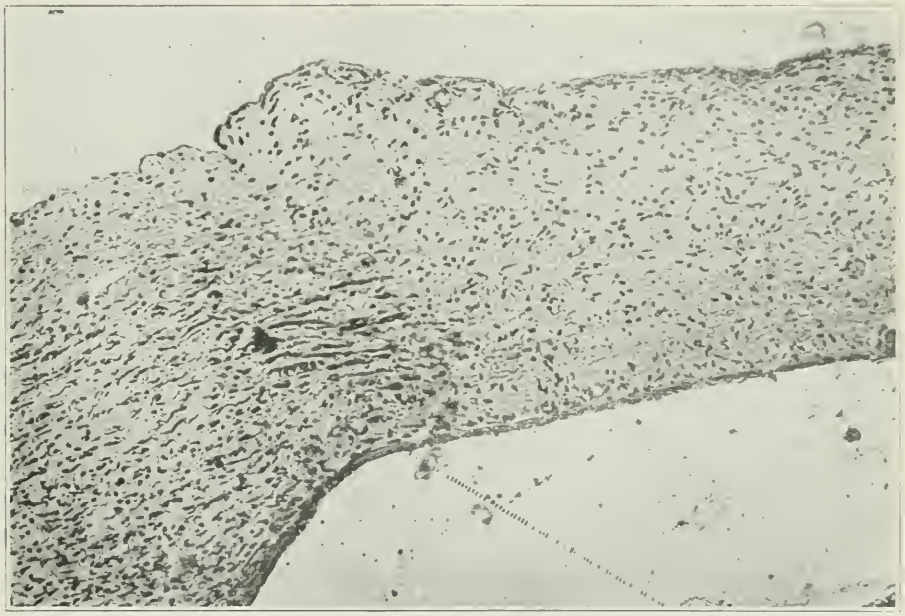

Fig. 18.—Section of sclerocorneal junction, three and one-half days after application of standard droplet. Infiltration of leucocytes, beginning fibroblastic and angioblastic proliferation.

less marked but the lids are thickened by the connective tissue proliferation. The membrana nictitans shows almost complete regeneration of its epithelium.

Five Days.—There is some regeneration of the corneal epithelium and proliferation of corneal cells and infiltration of leucocytes throughout the entire cornea. The edema of the bulbar conjunctiva is still very marked while that of the palpebral is very much less. The subconjunctival lymph follicles are very hyperplastic. Large dilated lymphatics show, however, in the subconjunctival connective tissue of the lids. The escharization of the epidermal side is very deep extending below the hair follicles, and there is no repair. In the lower lid the edema fluid shows marked fibrin formation.

Six Days.—Regeneration of the corneal epithelium over the limbus and extending in a delicate layer over the vertex. Endothelium of anterior chamber

is regenerating. Marked regeneration of the epithelium of the palpebral conjunctiva with overformation of epithelium. Regeneration less marked on the epidermal surface. Lymph follicles hyperplastic. The bulbar conjunctiva still shows marked edema without much cellular infiltration.

Seven Days.—(See Fig. 19.) Marked regeneration of the cornea with great thickening, the cornea being more than twice as thick as normal but the thickness varying in different portions. Marked infiltration of leucocytes and marked proliferation of the cells of the substantia propria. Around the periphery there is a marked formation of new blood vessels extending into the limbus and reaching nearly to the vertex. Marked regeneration of the endothelium of the anterior chamber. Sections cut in some planes of the cornea show a failure of regeneration of the corneal epithelium and a very marked infiltration of the anterior lamellæ. The conjunctival epithelium shows marked regeneration while the eschar of the epidermal portion of the lids has not yet separated. The bulbar conjunctiva still shows marked edema of the

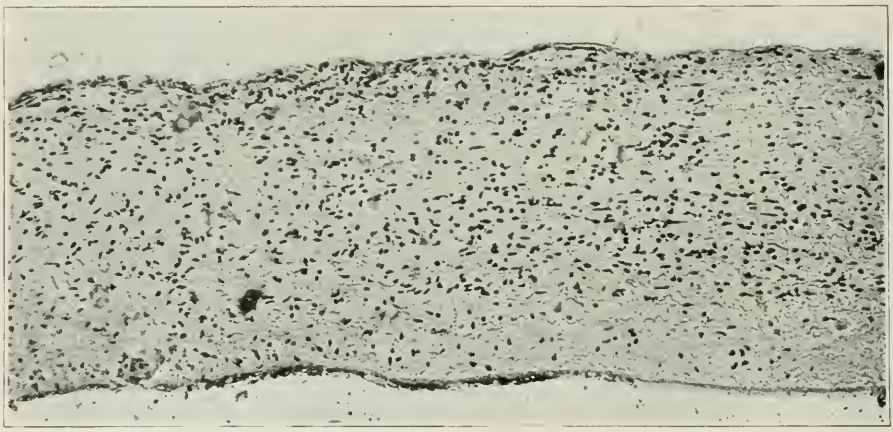

Fig. 19.—Section of corneal vertex seven days after application of standard droplet. Ulcerated surface. Infiltration of necrotic cornea with polynuclears and scattered fibroblasts. Beginning regeneration of endothelium.

subconjunctival tissue. The lids are thickened by the marked fibroblastic proliferation. There is intense congestion and many capillary hemorrhages.

Eleven and One-half Days.—Cornea thickened irregularly from leucocyte infiltration and proliferation of cells of the substantia propria. At the periphery the escharization is quite marked extending onto the bulbar conjunctiva, beneath which there is a marked leucocytic infiltration. The conjunctiva shows marked regeneration of its epithelium, with marked infiltration of the subepithelial tissue and marked hyperplasia of the lymph nodes. On the epidermal surface there is a very marked eschar formation which is partly adherent and partly separated. Beneath it there is marked regeneration of the surface epithelium and of the hair follicles. The membrana nictitans is markedly thickened, its epithelium nearly regenerated, and it shows a marked proliferation of new blood vessels with very hypertrophic endothelium.

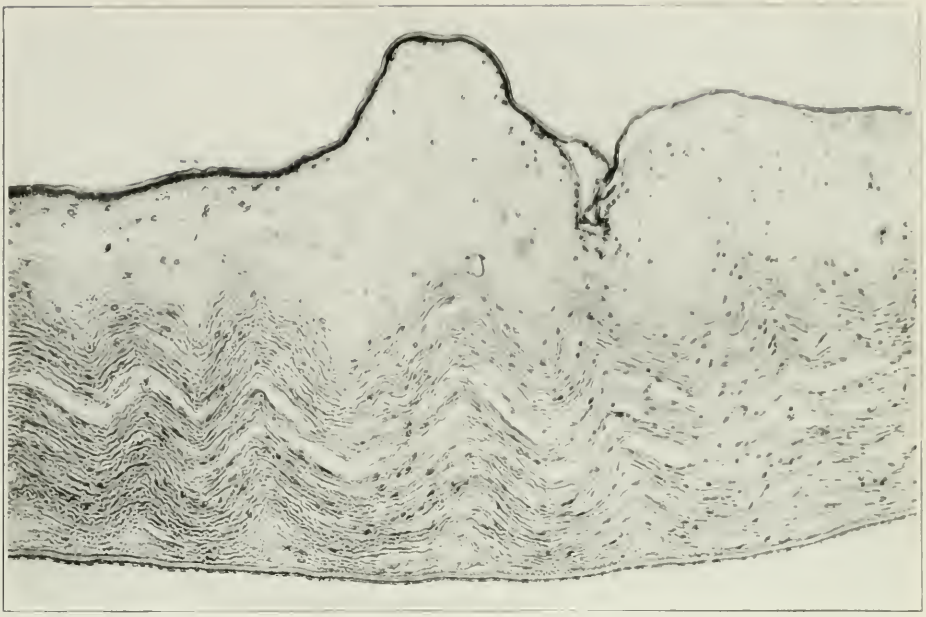

Fig. 20.—Section of corneal vertex four weeks after application of standard droplet, showing the marked irregularities in the corneal surface; regeneration of corneal epithelium and endothelium of anterior chamber; edema of the interstitial substance with some fibroblastic repair.

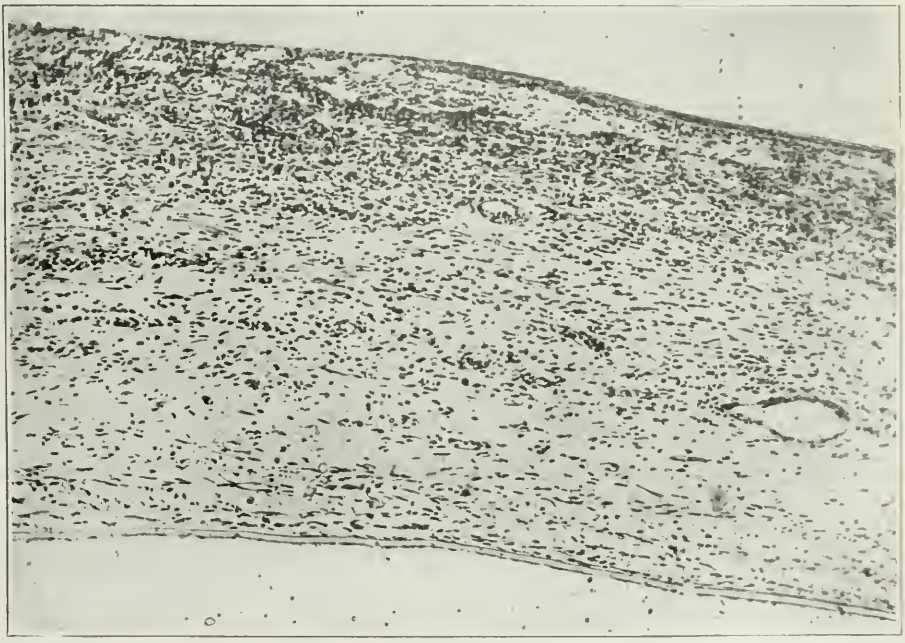

Fig. 21.—Sclerocorneal junction of same eye as in preceding figure, four weeks after application of standard droplet, showing vascularization and repair proceeding from the sclera.

Twelve and One-half Days.—Changes identical with the preceding. The hyperplasia of the subconjunctival lymph nodes is very marked.

Two Weeks.—Cornea very irregular in thickness. Shows less evidence of regeneration and repair than the preceding. New blood vessels extending into it from the periphery. Eyelids show marked regeneration of epithelium both on the conjunctival and on the skin side. Large nests of cells proceeding from the hair follicles.

Three Weeks.—Regeneration of corneal epithelium and endothelium of anterior chamber. Marked proliferation of blood vessels around the periphery of cornea and formation of scar tisue replacing the corneal substantia propria. Great irregularity in thickness of cornea. Eyelids show advanced repair and

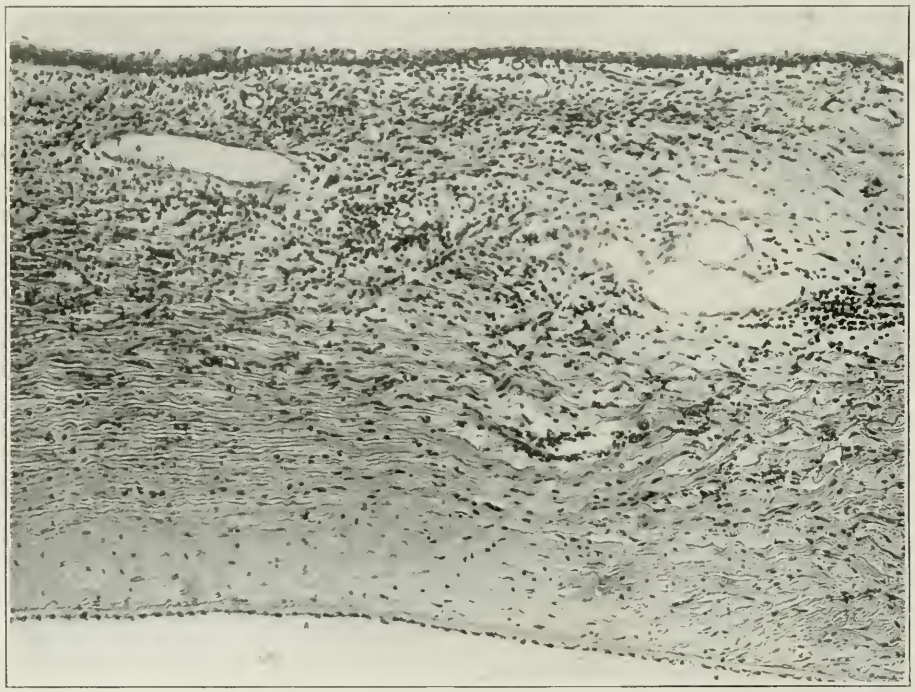

Fig. 22.—Section of corneal limbus four weeks after application of standard droplet. Advancing repair into the cornea from the sclerocorneal junction.

regeneration of the epidermal surfaces and of the conjunctival surface. Edema still present on the conjunctival side. The regenerating hair follicles and sebaceous glands form large atypical cell nests. The sinus hairs show fibroblastic obliteration of the cavernous spaces and atypical proliferations of squamous epithelium suggesting newly formed sebaceous glands.

Four Weeks.—(See Figs. 20, 21, 22.) The cornea shows throughout regeneration of its epithelium and of the endothelium of the anterior chamber. It is very irregularly thickened and has an uneven surface. From the periphery great numbers of newly formed vessels extend up toward the corneal vertex, on one side reaching half way across the cornea. These vessels are much more numerous on the anterior side of the cornea and many of them are very large

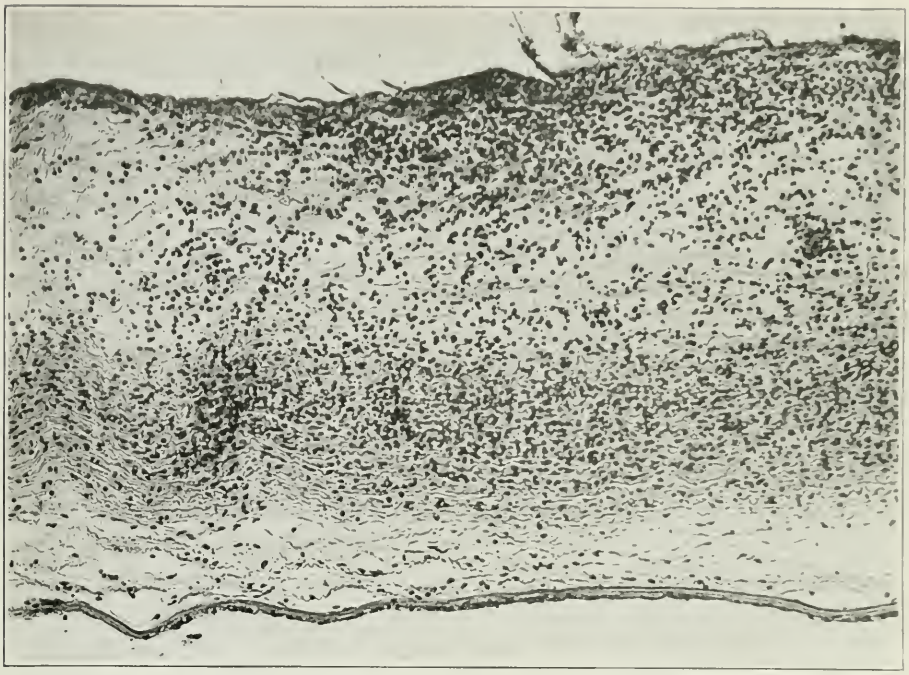

Fig. 23.—Section from the inferior portion of the cornea seven weeks after application of the standard droplet. Persistent ulcer; marked polynuclear infiltration of the cornea and repair. Blood vessels have reached the center of the cornea.

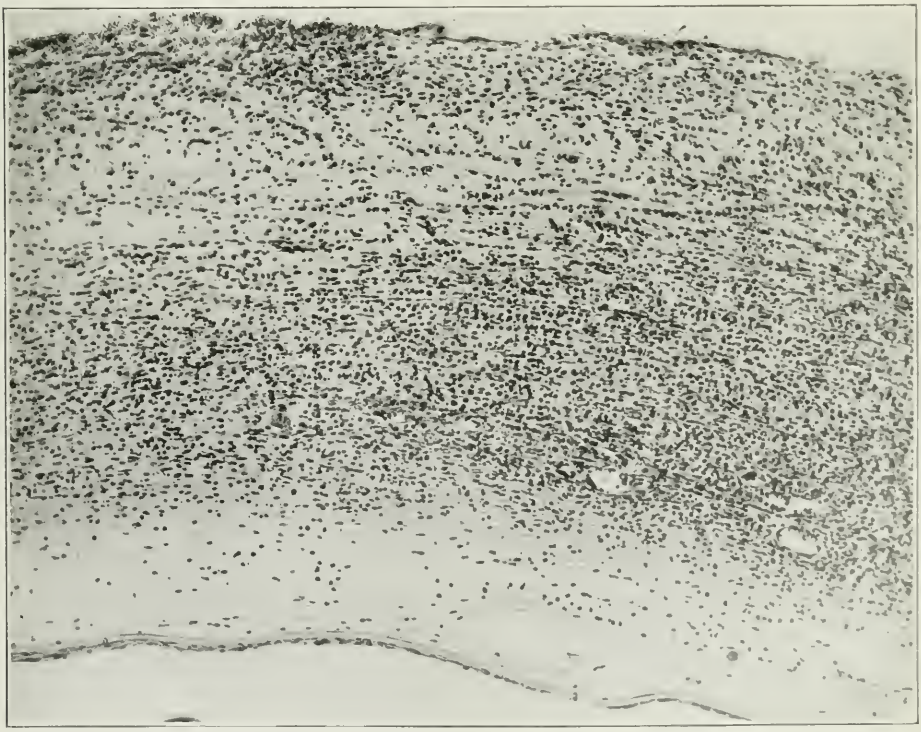

Fig. 24.—Section from inferior portion of corneal limbus, seven weeks after application of standard droplet. Partial regeneration of corneal epitheium. Marked polynuclear infiltration and advanced vascularization and repair of the substantia propria. Regeneration of the endothelium of the anterior chamber.

Fig. 25.—Section from the superior half of the corneal vertex seven weeks after application of standard droplet, showing the greater degree of cicatrization usually found in this portion.

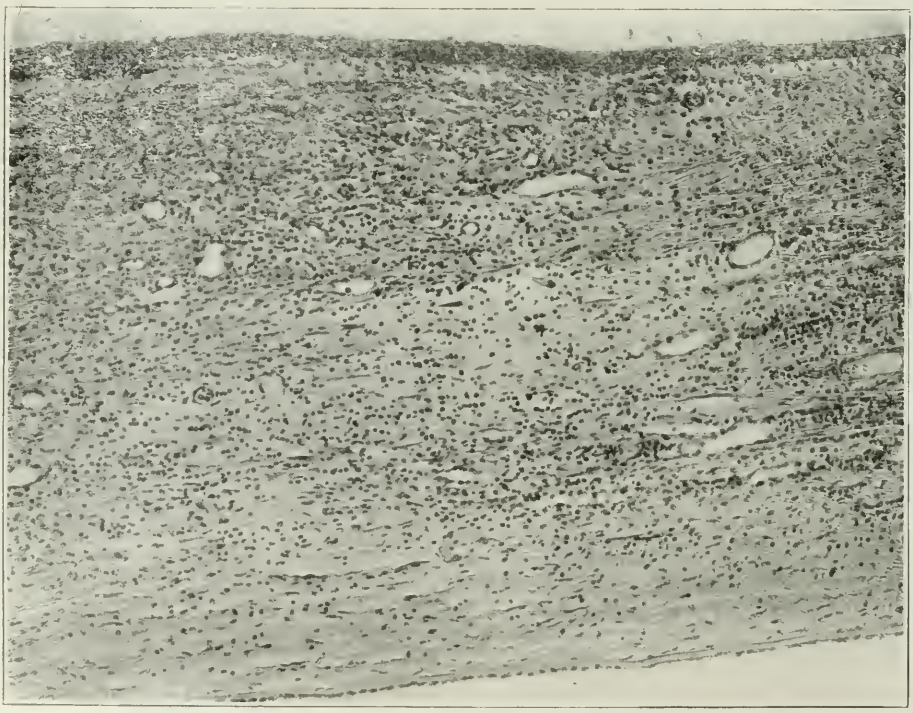

Fig. 26.—Section of corneal limbus from same eye as the preceding figure, showing advanced cicatrization.

and dilated. On one side near the scleral junction there is a large area of subepithelial edema infiltrated with leucocytes producing an elevation on the cornea as described in the gross notes. Other sections of the cornea show it to be heavily infiltrated with pus cells between the newly formed blood vessels. Regeneration of conjunctival epithelium is complete except near the palpebral margin where there is still an ulcer. Edema of the subjunctival tissues is much less marked than in the preceding. Harder's and the tarsal glands show marked lymphoid infiltration. Lacrimal gland more normal in appearance. Hair follicles show new formation of hairs. The large sebaceous glands at the palpebral margin are hyperplastic and the lymph nodes of the conjunctiva are also hyperplastic.

Seven Weeks.—(See Figs. 23, 24, 25, 26.) The cornea is markedly but very irregularly thickened throughout, heavily infiltrated with leucocytes and shows throughout its extent a marked new formation of blood vessels. Substantia propria is largely replaced by fibrous connective tissue. The membrane of Descemet shows as a clear hyaline line and the endothelium of the anterior chamber is regenerated in a flat layer over this. The regeneration of the epidermal surface of the lids is complete; the sebaceous glands are approaching normal size. The edema has almost entirely disappeared except over the bulbar conjunctiva. Lacrimal gland is still hypertrophic. Lymphoid tissue in Harder's gland is hyperplastic, as are also the subconjunctival lymph nodes. The lids and nictitating membrane are thickened from the new formation of connective tissue.

The Dog.—A smaller series was also carried out upon dogs. The changes are essentially the same in kind, although apparently of greater intensity. A marked hemorrhagic condition of the conjunctiva was noted in the earlier stages.

EXPOSURE TO DICHLORETHYLSULPHIDE VAPOR

The Rabbit.—Series of animals exposed for varying periods to varying concentrations of mustard gas vapor (1:20,000-1:50,000) and killed at intervals of twelve hours to four days after exposure in the gassing chamber showed precisely the same changes in kind as the animals treated with the standard droplet of the liquid. It was found that a fifteen minute exposure to a 1:20,000 concentration produced changes identical in degree with those produced by the standardized drop of liquid. It is noteworthy in these experiments with the weaker concentrations of the gas that the cornea first showed evidences of necrosis and then the skin surface of the lids, while the conjunctival epithelium did not undergo necrosis, and the conjunctiva itself presented only the picture of a mild conjunctivitis with an unusual degree of edema, particularly of the bulbar conjunctiva in the earlier stages, and of the palpebral in the later. The epidermal changes were in all cases much more severe than the conjunctival, marked necrosis of the former occurring when no necrosis of the conjunctival epithelium was observed. The corneal necrosis was always most severe at the corneal vertex. In all cases exposed to the gas the lesions are most intense in the portion of the conjunctiva and cornea exposed in the palpebral fissure, and

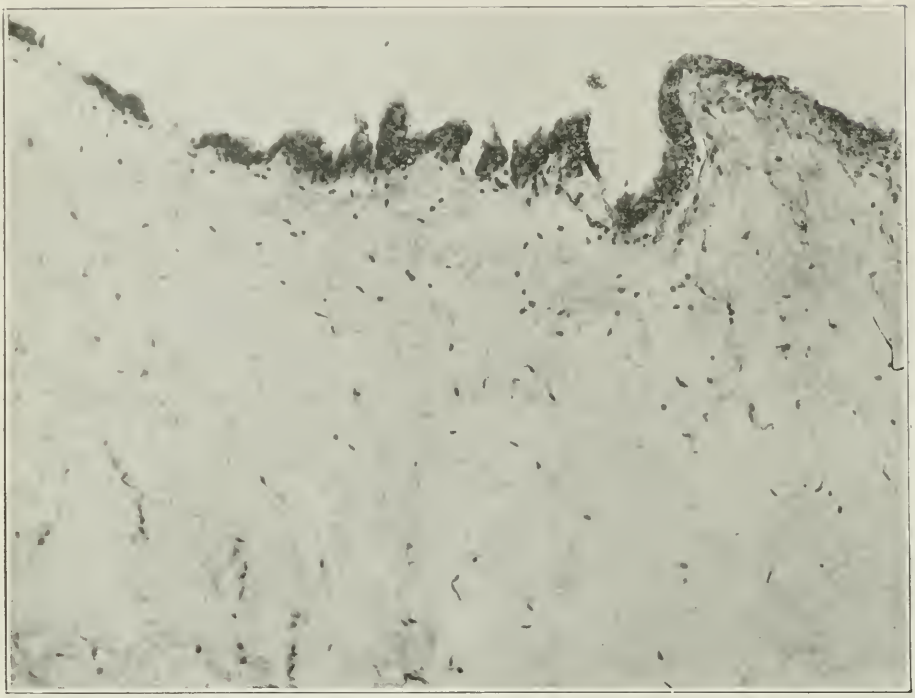

Fig. 27.—Bulbar conjunctiva two hours after application of standard droplet. Pyknosis of conjunctival epithelium and marked edema of the subepithelial connective tissue.

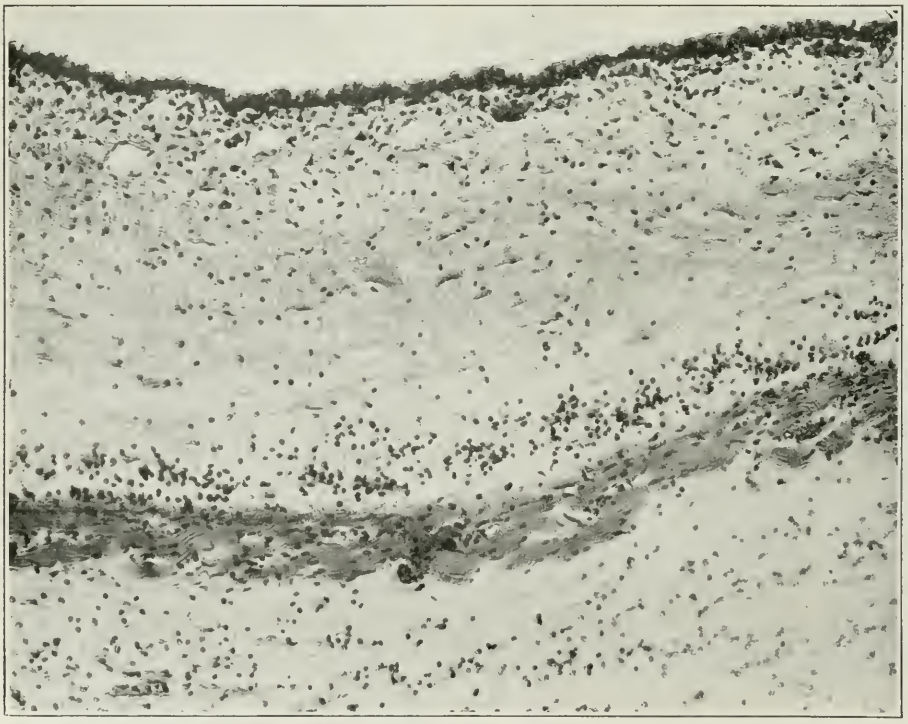

Fig. 28.—Section of palpebral conjunctiva five hours after application of standard droplet. Pyknosis of conjunctival epithelium. Edema of subconjunctival connective tissue. Polynuclear infiltration.

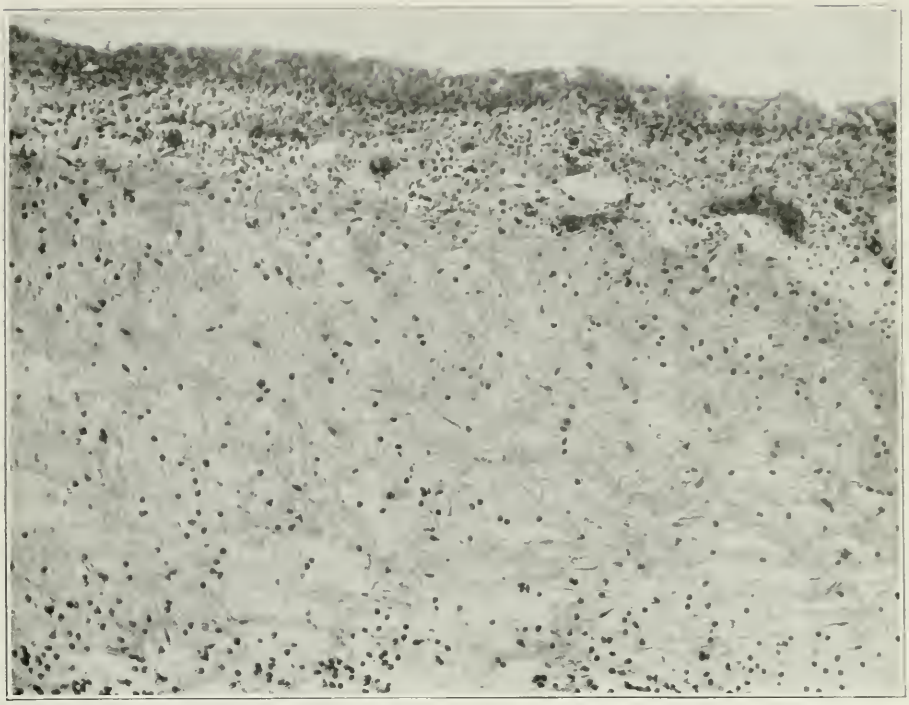

Fig. 29.—Section of palpebral conjunctiva eight hours after application of standard droplet. Complete necrosis of epithelium. Marked congestion. Minute hemorrhages. Polynuclear infiltration.

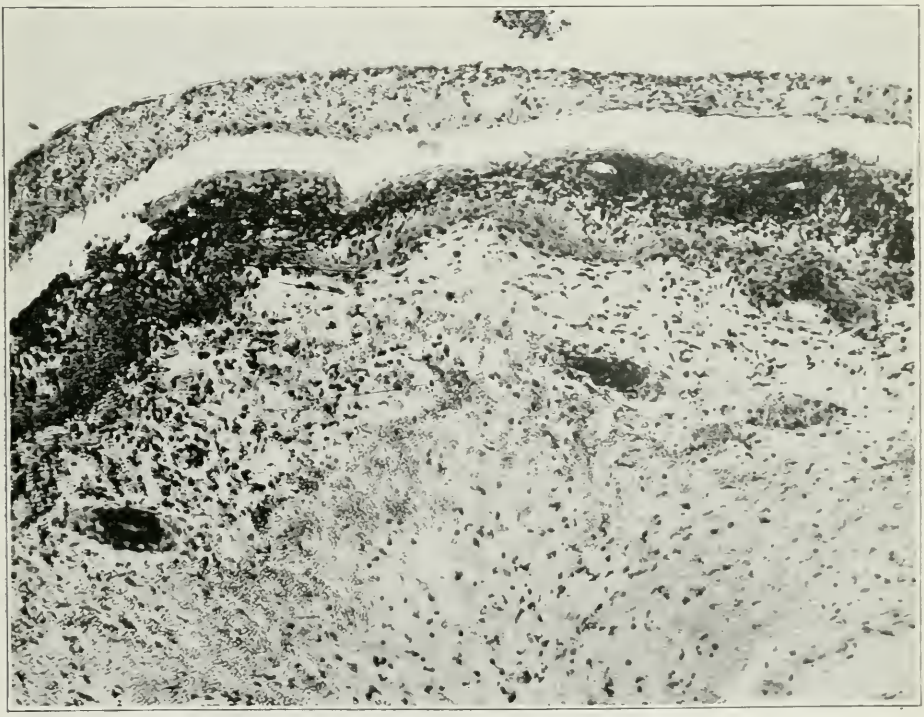

Fig. 30.—Section of palpebral conjunctiva just above the lid margin showing the fibrinopurulent exudate and greater degree of necrosis at this point.

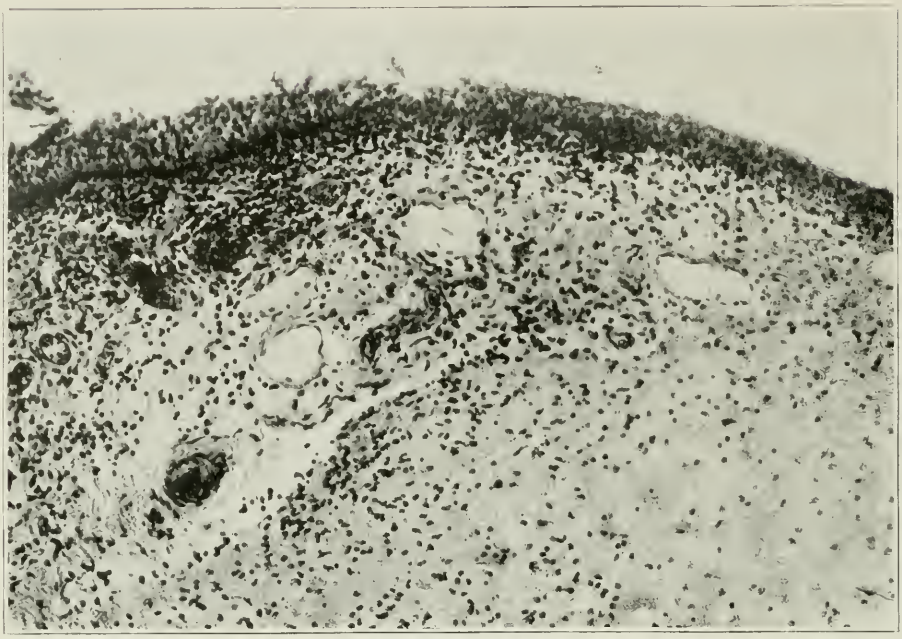

Fig. 31.—Palpebral conjunctiva twenty-six hours after application of standard droplet showing advancing necrosis, more marked infiltration, congestion, minute hemorrhages, and edema.

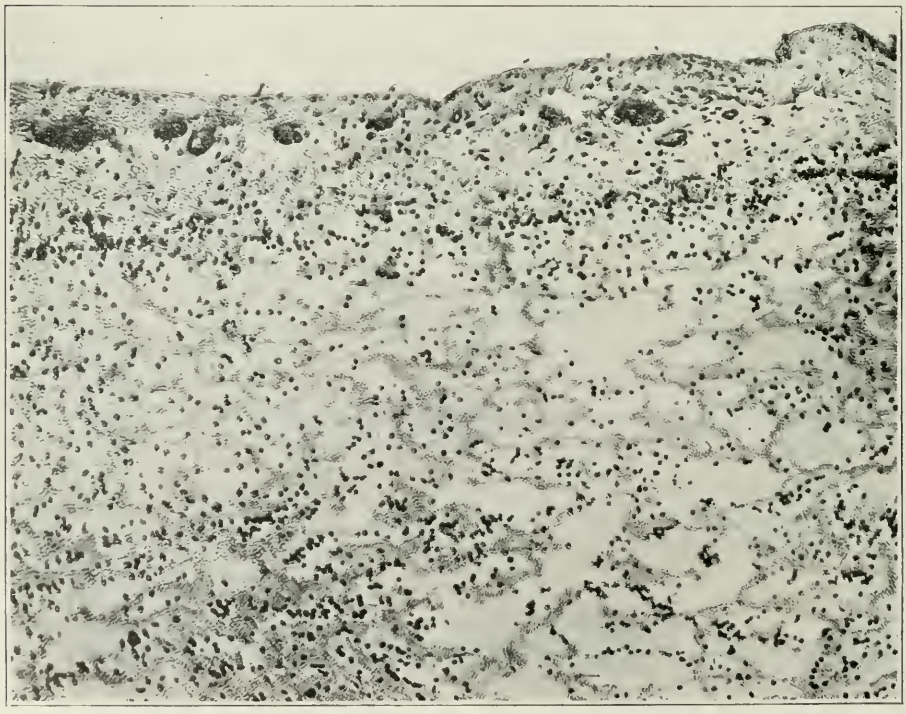

Fig. 32.—Palpebral conjunctiva thirty-four hours after application of standard droplet. Section at fornix of upper lid showing the complete loss of the necrotic surface, extreme edema and polynuclear infiltration.

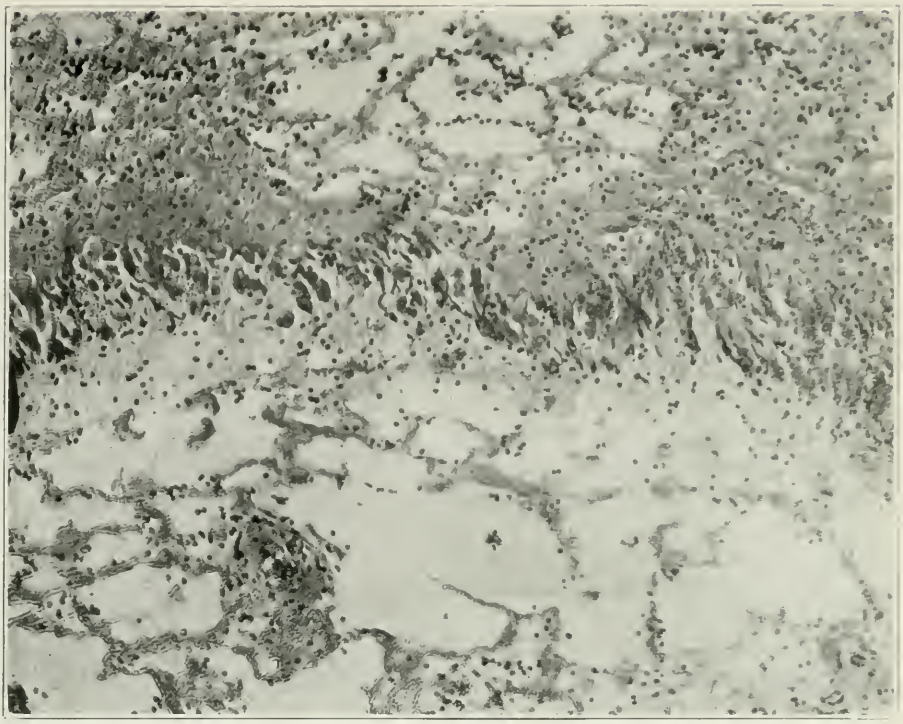

Fig. 33.—Section from the same region as in the preceding, but taken deeper down, showing the extreme edema and liquefaction necrosis, below the narrow band of the sphincter orbicularis.

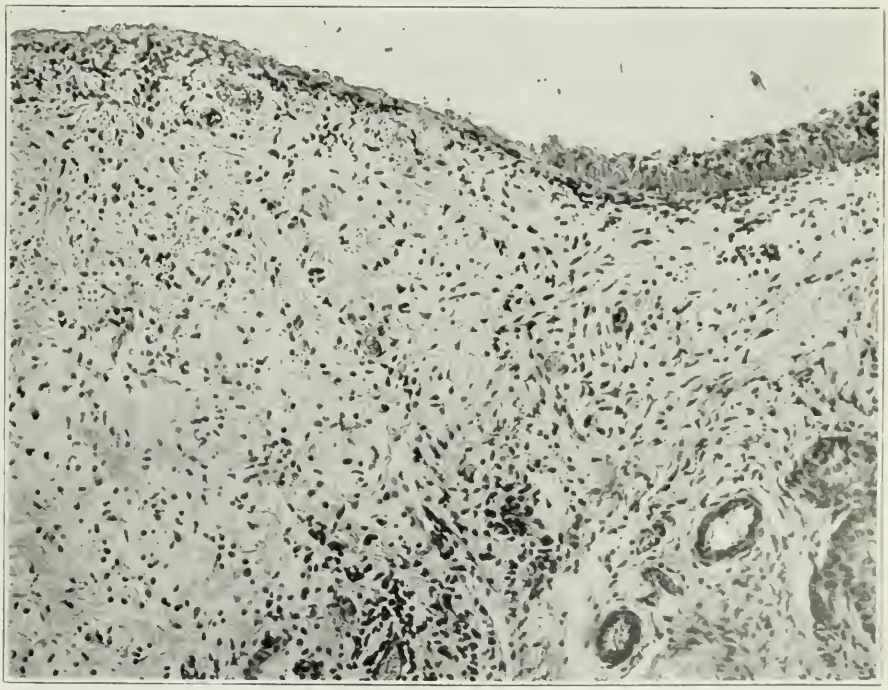

Fig. 34.—Section of upper lid at palpebral margin four days after direct application of standard droplet. Advanced ulceration, beginning repair.

the lesions therefore are much less diffuse than when direct application is used, thus resembling more nearly the human cases.

DIRECT APPLICATION OF MUSTARD GAS LIQUID TO THE EYES OF DEAD ANIMALS, THE EYES SO TREATED BEING EXAMINED AT INTERVALS

Microscopic examination of eyes, to which dichlorethylsulphide had been applied postmortem, shows no changes attributable to the action of the mustard gas liquid.

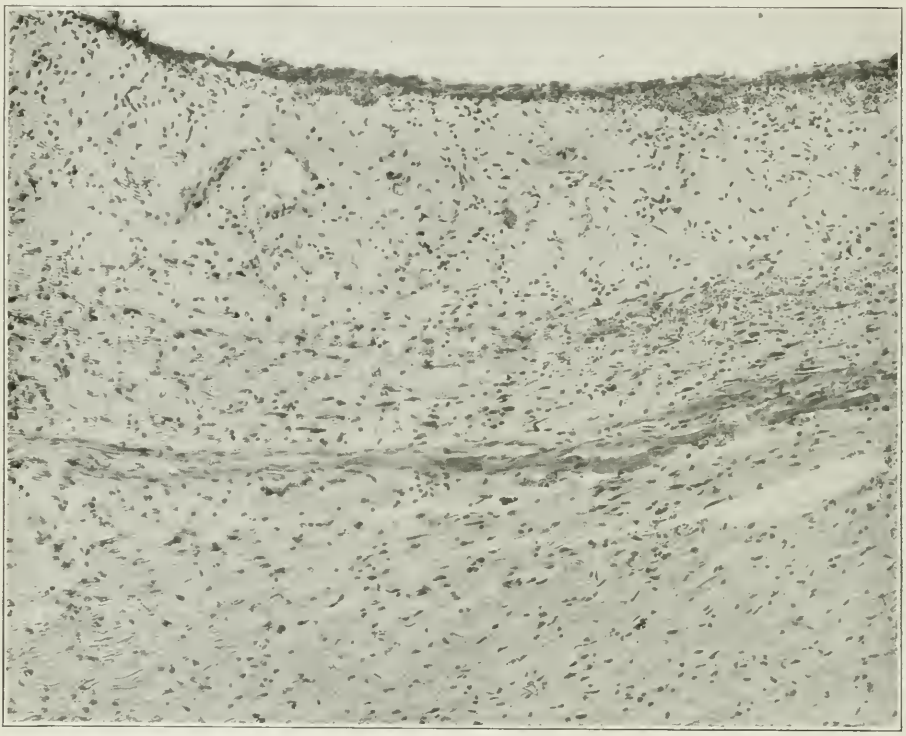

Fig. 35.—Section of same lid near fornix. Regeneration of the conjunctival epithelium. Disappearance of the edema and advancing cicatrization of the subconjunctival tissues.

EYES OF ANIMALS RECEIVING SUBCUTANEOUS AND INTRAVENOUS INJECTIONS OF DICHLORETHYLSULPHIDE

Animals so treated died within five hours after the intravenous injection of one minim and uniformly, in four to five days after the subcutaneous injection of one minim. Microscopic examination of the eyes of these animals shows no evidence of conjunctivitis or other lesions.

EYES SHOWING SECONDARY INFECTION

Four cases showing panophthalmitis, three at five weeks and one at six weeks, show microscopically a diffuse suppurative process involving all the structures of the eye and of the orbit. The suppurative process begins first in the cornea, and in the earlier stages may show as small pinpoint abscesses

in the substantia propria, each surrounding a colony of cocci. The process extends through the anterior chamber toward the posterior portion of the eyeball until ultimately all is involved. Similar changes are observed in a dog three weeks after exposure, the earlier infection in this case resulting from the lack of care and the lessened resistance of this especial animal.

CHANGES IN ORBITAL TISSUES

In the uninfected cases these consist of congestion and edema, and a mild diffuse inflammation, involving particularly the ocular muscles. In the infected cases there is a diffuse suppurative process.

Summary of the Microscopic Pathology

1. The microscopic changes produced by the direct application of the standard droplet of the liquid and by exposure for fifteen minutes to a vapor concentration of 1:20,000 are identical.

2. *Changes in the Cornea.*—The earliest changes noted are in the cornea, consisting of pyknosis and contraction of the epithelium and of the substantia propria, most marked at the corneal vertex and extending to Descemet's membrane. This is followed by a loss of nuclei until by the twelfth hour the corneal vertex shows complete necrosis, the necrosis often extending through the limbus nearly to the scleral junction. Desquamation of the dead corneal epithelium begins in about five hours. Polynuclear infiltration of the sclerocorneal junction begins in five to six hours. Fibroblastic proliferation was first noted at thirty-four hours at the sclerocorneal junction. Earliest signs of regeneration of the corneal substantia propria were noted at the periphery at sixty-five hours. New formation of blood vessels into the limbus was well marked as early as seven days. Slow repair of cornea continues for several weeks with development of a highly vascularized corneal cicatrix. Marked changes in the corneal thickness occur as the result of separation of the lamellæ, edema, cellular infiltration and fibroblastic proliferation. The severity of the corneal lesion is in direct proportion to the concentration of the gas and the period of exposure.

3. *Changes in the Conjunctiva.*—Necrosis and desquamation of a large part of the conjunctival epithelium results, but it is noteworthy that this necrosis is much less in degree than that of the cornea or of the skin surfaces of the eyelids. The primary necrosis rarely extends beneath the basement membrane of the palpebral and bulbar conjunctiva, except at the palpebral margin where collections of a serofibrinopurulent exudate take place. Here shallow ulcers are produced. The most striking feature of the conjunctival involvement is the extreme edema of the subconjunctival connective tissues which is usually most marked in the bulbar conjunctiva near the scleral sulcus and in the palpebral conjunctiva of the upper lid. This is so extreme that liquefaction necrosis in this tissue, with marked leucocyte infiltration, usually follows. Petechial hemorrhages are of frequent occurrence in the subconjunctival connective tissue. Regeneration of the conjunctival epithelium occurs readily and

healing takes place with a permanent thickening of the conjunctiva due to the formation of fibroblastic tissue.

4. *Structures of Eyeball.*—(See Figs. 46, 47.) Iritis and iridocyclitis with exudation into the anterior chamber, occur without infection in the severest forms of gassing; and are common occurrences at about the third to sixth week in the uncared-for cases as the result of secondary infection even when the gassing was light. In the cared-for cases of average exposure, no changes were observed in iris, ciliary body, chorioid, retina and optic nerve, except congestion and edema.

5. *Nictitating Membrane.*—Changes observed in rabbits are necrosis of the epithelium, extreme edema, multiple hemorrhages, congestion, and eventually more or less marked thickening from connective tissue proliferation.

6. *Lacrimal Gland.*—Increased functional activity was noted at all times; ultimately, overuse atrophy and subsequent hypertrophy. Increased albumin content was observed in the secretion.

7. *Harder's Gland.*—Parenchymatous degeneration and inflammatory infiltration occurred.

8. *Tarsal Glands.*—Evidences of penetration into the tarsal glands were shown by degeneration and necrosis of certain of the acini. Leucocyte infiltration occurred about and into these glands.

9. *Skin Surface of Eyelids.*—The same changes were observed in the cutaneous surface of the eyelids as were described in our paper on cutaneous lesions. The important influence of the sebaceous glands and hair follicles in permitting the entrance of the gas into the deeper tissues of the dermis is strikingly shown here, the penetration into and resulting escharization of the skin being greater than in the case of the cornea or the conjunctiva.

10. The relatively slight penetration into the subconjunctival tissues may be explained as the result of the protection afforded by the moistness of the surface and lacrimation.

11. *Orbital Tissues.*—In the cared-for cases congestion, edema and a mild diffuse cellular infiltration, particularly in the orbital muscles was noted; in infected cases a diffuse suppurative cellulitis occurs.

III. CLINICAL CASES

(For the opportunity of examining the clinical cases, and for their histories, we are indebted to Capt. L. L. Roos.)

Case 1.—(See Fig. 36.) Exposed to strong concentration of mustard gas vapor for 10 to 12 minutes. Patient wore a gas mask.

The eyes began to burn and be painful, lacrimated freely, and were red and inflamed two hours after exposure. Three to four hours after exposure he began to feel as though there were granules beneath the eyelid. He could not keep his eyes closed because there was much more pain when the lid borders were approximated. He was very sleepy, because of much loss of rest due to night work, and his eyelids felt heavy.

He went to bed. Boric acid compresses (cold) were applied. American

oil was instilled once; it did no good. The compresses were to be continuous, they relieved the pain, but he could bear them only about one-half hour at a time, through the night. For three to four days argyrol was instilled once in 24 hours after exposure, and did very little good. The palpebral conjunctiva appeared "blistered" the morning after the exposure.

The irritation continued for three to four days but gradually decreased in severity. The congestion decreased but was still marked. In fact it was present and quite distinct thirty-one days after exposure.

The patient complained of "misty" blurring of vision which was marked at first and has decreased also, but was still present three weeks after exposure. The bright sunlight hurt his eyes, the lids felt heavy.

There was no interference with accommodation so far as the patient knew. He was able to read about the tenth day, but could only read a page at a time.

Examination.—Congested dilated vessels on the bulbar conjunctiva from the border of cornea, over the limbus, to the inner and outer canthus in each eye. The congestion and thickening of the bulbar conjunctiva showed in the palpebral aperture which is really exposed bulbar conjunctiva when the lids are in their normal position, open. The palpebral conjunctiva, especially superiorly, shows slight thickening.

CASE II.—(Fig. 37.) Exposed ten to twelve minutes to a strong concentration of mustard gas vapor. He wore at the time a gas mask.

Sulphur dichloride and sulphur monochloride have always irritated his eyes. He first noted irritation under the arms about four hours after exposure, and just one hour later, that is, five hours after exposure, there was a stinging irritation "just like salt" in the eyes. One drop of "Silvol" solution was put in each eye. This increased the pain. The eyes lacrimated profusely, and the eye-balls were red, and the vessels congested. Boric acid compresses (cold) were applied at intervals all night. At 3 A.M. he found that he could only open his eyes to a slight extent, the aperture was only about ½ inch at the greatest. The lids were edematous and this prevented the opening of the eyes. The morning after the exposure the eyes were completely closed and the lashes were "glued together" by the thick purulent exudate. He could not open the eyes wide enough to see anything. At the first-aid room argyrol and sterile American oil were put into the eyes and he was put to bed and cold or iced boric compresses were put on continuously for 5 days. Argyrol was instilled 3½ days after exposure for about 30 minutes and everything both near and far was found to be blurred. The conjunctiva was congested. For more than 10 days the eyes lacrimated profusely, especially the left eye. On the fifth day his vision was clearer but very much impaired. He could not see endings of words or letters at all on a printed page. He could not read ordinary print for ten days and then he could only read the print for 10 minutes at a time until the eyes ached, and things became blurred.

It was not until the eighteenth day that he could read for an hour at a time. His vision for distance has gradually improved but is still somewhat blurred. At the end of the third week near vision is such that he can as yet

not read much more than one and a half hours at a time and then he must rest two to three hours.

Examination.—Thickening of the conjunctiva in the palpebral fissure is especially marked in the triangles with apex at the inner canthus and base at the inner limbus. The thickened conjunctiva is yellowish. The vessels are slightly congested. The palpebral conjunctiva is not very much changed, possibly slightly thickened.

Case III.—Exposure of 40 minutes in 4 shifts to strong concentration of mustard gas vapor while wearing a gas mask.

The eyes had been congested for two days because of exposure to hydrochloric acid gas. On entering the infirmary at 6 P.M. he had no eye symptoms but because of the congestion the eyes were irrigated with sodium bicarbonate solution or boric acid. He was very nauseated and sick, and vomited, and retched very much. At the same time he complained of severe sharp pains in the eyes.

Boric acid compresses were applied continuously for three days and the eyes were washed with the boric acid about every fifteen minutes for the entire first night. The eyes were very painful, burned and felt as though an electric current was passing across and through the anterior part of the eye. The eyes were swollen and a purulent exudate glued the eyelashes down. On the third day while his eyes were being opened and argyrol instilled he had a flash of vision for a second, just long enough to see his nurse. On the fourth day he recognized individuals. He had been able to open his eyes about the fourth night, but he could only see a dull light. On the fifth day he opened his eyes slightly and everything was blurred, near and distant; vision was likewise impaired.

He was not able to read for about fourteen days, and then only for about five minutes at a time, gradually becoming able to read more and more, but at present he can read only about one to two hours at a time. When in the sunlight, however, there is a feeling of "wideness" (of the palpebral opening), some blur, and some discomfort, and slight photophobia.

Examination.—In the morning there is slight purulent exudation which glues the eyelashes together; there is a small drop of purulent exudate in the inner canthus. There is a slight blepharitis marginalis. The ocular conjunctivæ show the thickened, slightly yellowish, elevated areas, pingueculæ, on either side of the corneæ. The vessels are large, slightly dilated and congested.

The palpebral conjunctiva shows nothing of any great interest.

Case IV.—(See Fig. 38.) Exposure of 30 minutes to strong concentration of the vapor of dichlorethylsulphide while wearing the gas mask.

He was first exposed at about 3:30 P.M. and noticed his first symptoms at about 5 P.M. There was irritation, burning and lacrimation of the eyes and a "faint feeling" in the pit of the stomach. Then on leaving the infirmary and getting into "the air" the eyes felt better and he was not troubled until he returned to the infirmary. Here after taking the routine "shower, kerosene rub and shower," treatment and retiring, his eyes felt very painful with the sensa-

Fig. 36.—Congestion of the conjunctival vessels persisting to a marked degree, four weeks after exposure to dichlorethylsulphide vapor.

Fig. 37.—Persistent congestion four weeks after exposure to dichlorethylsulphide vapor. Acute symptoms were very severe and the patient still complained of dimness of vision when he left the hospital after five weeks.

Fig. 38.—Marked conjunctival congestion and hordeolum of left upper lid in a case of severe mustard gas conjunctivitis. Four weeks after exposure. The hordeolum is a part of the general staphylococcus furunculosis which may characterize the later stages of the severe skin burns.

Fig. 39.—Dichlorethylsulphide conjunctivitis four weeks after exposure to vapor. In the acute stage there were extreme photophobia, lacrimation, pain, edema and purulent exudation. The residual congestion and seropurulent exudation are still evident.

tion of fine sand under the lids and there was profuse lacrimation. A thick serous exudate made the eyelashes mat together and seal the eye.

His vision was blurred, probably due to the increased lacrimatory secretion. The eyes were red and congested, according to his roommate. His eyes were irrigated with boric acid; American oil was instilled and cold boric acid compresses were applied continuously for five days. Argyrol was used from the second day until about the fifth day.

The eyes could not be opened, because the lids were swollen, edematous, and glued together at the margins by the matted lashes.

After the third day he was able to hold the eyes open for a few minutes at long intervals, but it was not until the fifth day that he could dispense with the compresses. His vision had always been very blurred, but cleared fairly well on the fifth day. There was some yellowish exudation with considerable serous exudation. The eyes were washed frequently during the day with boric acid solution.

A hordeolum formed on the upper eyelid near the inner canthus, on about the fourteenth day.

The patient did not attempt to read for two weeks and when he did begin he noticed no trouble, except that the eyes ached after he had read a quarter to half an hour. He could not read magazines until about the tenth day.

Examination.—The bulbar conjunctiva shows the same features as in the other cases but to a more marked degree; there is a thickening and a yellowish change, with marked congestion of the vessels of the part of the conjunctiva that is exposed in the palpebral fissures, on either side of the corneæ. At the limbic border a number of straight, small, deep vessels were seen to be injected and suggested a deeper penetration and a sclerociliary injection. The conjunctiva from the inner limbus to the inner canthus is more markedly involved.

Case V.—(See Fig. 39.) Exposed thirty to forty-five minutes in several shifts to strong concentration of dichlorethylsulphide vapor, while wearing gas mask.

Began on the evening shift at 4 P.M. and first exposed himself at this time. He noticed no eye symptoms until about 10 P.M. when there was burning, a feeling as though granules were under the lids, and a fairly profuse lacrimation. Cold boric acid compresses, boric acid eye washes, etc., were employed during the night and for several days. The routine treatment, as given, together with argyrol instillations was employed. According to the physician in charge, the patient was in severe shock.

There was some pain, blurred vision for near and distant objects, and a profuse lacrimation. At first the lacrimation was serous in type, but soon it became yellowish, thicker and almost purulent. The lids were tightly sealed and somewhat edematous.

The symptoms continued to be fairly severe and the treatment was kept up for about a week. It was not until this time that the vision was at all clear. The lacrimation has continued.

The patient has not attempted to read as yet though he has had no trouble with his vision for about twelve to fourteen days.

Examination. Slightly congested areas in the palpebral aperture on each side of the cornea. The conjunctiva shows slight thickening in the same exposed areas. The discharge from the collection of the pus is found both in the inner and in the outer canthi. The palpebral conjunctiva shows nothing of significance.

CASE VI. (See Fig. 40.) Exposed 45 minutes in several shifts to strong concentration of mustard gas vapor, while wearing gas mask.

The irritation of the eyes began at about 9 P.M., some five hours after exposure. There was severe burning and a feeling of sand and glass scratching in the eyes.

There was profuse lacrimation and congestion. The next morning after the exposure the exudate from the eyes was seen to be more or less purulent and glued the eyelashes together, and held the eyes closed.

After the parts had been treated with cold boric acid compresses during the whole first night as had been done in all the cases it was necessary to "flush" the eyes with the solution in order to dissolve and loosen the plastic purulent exudate. When opened the eyes were found to be much congested and small blebs were seen especially on the lower palpebral conjunctiva. Argyrol was instilled as in the other cases and continuous compresses were applied for five days. The eyes were opened for short spaces of time on the fourth and fifth days and a blurring and dimness of vision was noted. The patient has not attempted to read as yet because of his severe general condition, but he has noticed no symptoms on the part of his eyes since the end of the first week of his trouble.

Examination.—Shows the same condition that has been found in the other cases. The acute congestion has decreased and the signs remaining are those of a somewhat chronic irritative process. There is the slight thickening in the exposed part of the bulbar conjunctiva in the palpebral fissure.

CASE VII.—Exposed directly to strong vapor.

The vapor irritated the eyes severely and caused pain and lacrimation for ten to fifteen minutes. There were no blebs but there was some congestion. After this there was no more pain and the patient continued to work where there is practically always some vapor.

The patient's eyes were not painful but became more and more congested.

Examination.—The whole conjunctiva was inflamed, congested and slightly edematous, the lacrimation was increased in amount. The vision was apparently not involved. The bulbar conjunctiva was more markedly congested and affected than was the palpebral. Under the boric-acid-continuous-compress treatment, there was a decided improvement, the congestion was fairly well relieved in about four days. (Picture taken on fifth day.)

On fifth day the area which is most markedly injected is in the bulbar conjunctiva of the palpebral fissure. Some of the scleral vessels in this region are injected. The small subcutaneous fatty area (pinguecula) is present.

Case VIII.—(See Fig. 41.) Exposed to fumes of ethyl alcohol, ethylene and some dichlorethylsulphide.

The eyes showed chronic irritation, thickening of the bulbar conjunctiva in the palpebral aperture, and some yellowish discoloration and areas that appeared to be fatty deposits.

Fig. 40.—Dichlorethylsulphide conjunctivitis four weeks after exposure to vapor. The severity of the original process is indicated by the severe skin changes. The persistent congestion is the sole evidence of the severe conjunctivitis that was present.

Fig. 41.—Repeated exposures to a low concentration of mustard gas vapor. Persistent congestion. Pigmentation of the sclera in the palpebral fissure. Yellowish pigmented elevation of the conjunctiva near inner segment of limbus of the nature of a pinguecula.

Fig. 42.—Conjunctival congestion and pigmentation of the sclera limited to the exposed area in the palpebral fissure of a patient subjected to low concentrations of mustard gas vapor over a relatively long period. Gave no history of a severe acute process.

The patient complains of impaired vision. He has had one severe arm burn but there were no eye symptoms at that time.

At present he complains of lacrimation and blurring of vision.

Case IX.—(See Fig. 42.) There has been a slight irritation and itching and some congestion of the conjunctiva for about two weeks. At first the symptoms were very mild and noticeable only after exposure to dichlorethylsulphide. The symptoms were exaggerated and prolonged if the patient sat

through a moving picture show. Bright sunlight also increased the symptoms.

The conditions have been more or less cumulative and the symptoms have gradually increased. During the past week, he has had lacrimation, congestion of the bulbar conjunctiva in the palpebral fissure and difficulty in accommodation in the right eye with more or less blurring of vision.

There is also some sticky seropurulent exudate, and in the morning the eyelids and lashes are glued together, and a drop of pus is seen in the inner canthus. He has used only the boric acid wash.

Examination.—Shows a picture similar to the others, with a thickening of the conjunctiva of the eyeball that is exposed in the palpebral fissure. The right eye shows slightly more congestion and thickening than the left and there is some ciliary injection about the sclerocorneal junction.

The palpebral conjunctiva, especially over the lower right eyelid, shows some congestion and slight thickening.

Case X.—Exposure without mask to strong concentration of mustard gas vapor. Symptoms developed three hours later.

He complained of severe irritation and pain in the eyes and the lids were swollen, edematous and could hardly be separated. The routine cold boric acid compresses were used, and it was not until three days later that the edema disappeared.

Case XI.—Presented a somewhat different aspect. He was exposed for a short time, a few minutes, to quite a heavy dose of dichlorethylsulphide vapor. He had some slight irritation and lacrimation but no congestion to any marked degree. There was, however, a diminution of vision in the right eye which was said to be very marked. Both near and far vision were greatly reduced. There was blurring of all images.

Report of Eye Specialist.—"In regard to Case XI, whom I this day examined, I find his vision in right eye 4/200. Under atropine I find he has at least three diopters of hypermetropia with some astigmatism, the correcting of which does not improve his vision.

"If this condition has been brought about in the last three weeks as he claims, though the fundus does not show this, it must be toxic. Otherwise, it is amblyopic and his previous vision was not normal."

Case XII.—Has been exposed to dichlorethylsulphide for about one month. He has had some irritation and congestion about one week ago. At present the condition appears to be much improved but the patient comes in complaining of failing vision, dimness and blurring. Both eyes are affected and the condition is progressing rapidly; both near vision and distant vision are involved. The patient must bring a printed page to within six inches of the eye in order to be able to read.

A close examination of the corneæ failed to reveal any opacities to account for the trouble. The corneal epithelium showed no apparent thickening or dulling. The conjunctiva shows some thickening and signs of chronic irritation in the part exposed in the palpebral fissure. It was considered that this case like

Case XI was one of some internal fundus pathology or an accommodation disturbance.

Case XIII.—Exposure of 1 hour to very dilute concentration of mustard gas vapor.

Six hours later marked burning and irritation of conjunctiva, lacrimation, blurring of vision and reddening of conjunctival surfaces. These symptoms lasted three days and gradually decreased, but a feeling of roughness of lids and visual disturbance persisted for nearly two months.

CLINICAL SUMMARY

From these cases it will be seen that exposure to varying concentrations of vapor of dichlorethylsulphide for varying periods produces a conjunctivitis showing all stages and degrees of intensity from a simple acute type to a severe

Fig. 43.—Five weeks after direct application of dichlorethylsulphide to cornea. Dosage about twice the size of the standard droplet. Lids not separated. Eye untreated. Resulting purulent panophthalmitis with collapse of eyeball.

chronic proliferative conjunctivitis. The symptomatology and clinical picture may vary greatly. The lesions are most marked in that portion of the bulbar conjunctiva exposed in the palpebral fissure. The milder cases recover after several days or weeks, but the more severe cases develop chronic hyperemia of the conjunctiva, new formation of vessels and scar tissue in the most severe, with more or less permanent disturbances of vision. One of the cases observed developed an almost complete amblyopia in one eye, so that only the perception of light and shadows was possible. In another case marked bilateral gradual reduction of vision was noted. A xanthoma-like pigmentation was also noted in the chronic cases, the pigmentation developing near the outer or inner sclerocorneal junction, or over the corneal limbus.

There is no evidence of any metastatic involvement of the eye. In cases

showing severe burns of other parts of the body, arm, leg, etc., no conjunctivitis, even of the simplest type, developed. Such exceptions are explained entirely by the fact that the vapor did not reach the eyes externally. In other cases with severe burns over the entire body with the exception of the face, which was protected by the gas mask, no eye or conjunctival symptoms were noted.

Fig. 44. Right and left eyes of a rabbit 54 hours after 12 hours' exposure in gas chamber to a concentration of 1:50,000 of dichlorethylsulphide. Right eye received prophylactic treatment with dichloramine-T, 0.5 per cent in chlorcosane. Left eye untreated. Right eye shows much less marked corneal necrosis, the area of necrosis being sharply demarcated by the somewhat approximated borders of the palpebral fissure. The characteristic line described by Pissarello shows beautifully. The left eye shows the usual diffuse necrosis of the cornea.

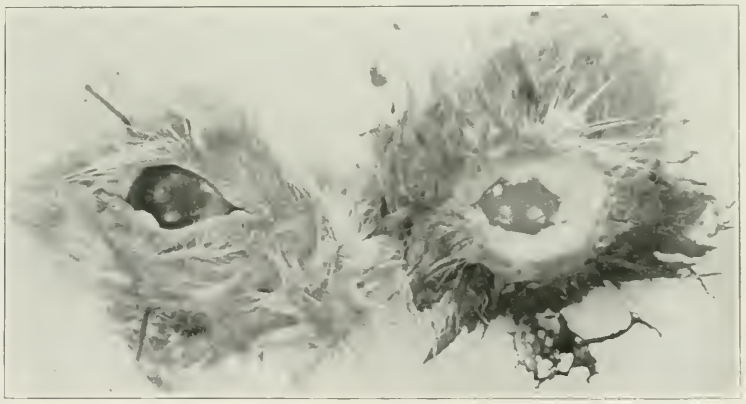

Fig. 45.—Right and left eyes of rabbit gassed at the same time as the preceding. Right eye treated with four applications during the first 36 hours of dichloramine-T, 0.5 per cent in chlorcosane. Died 96 hours after end of exposure. Right eye shows less edema and much less marked corneal injury; left untreated for 60 hours, at end of which time some purulent exudate formed. Left eye, entirely untreated, showed the usual marked edema and corneal necrosis, with marked purulent exudation.

IV. TREATMENT

Inasmuch as the routine and universally employed clinical treatment accorded the cases, as described above, seemed to us unsatisfactory, experimental investigation was carried out with a hope of obtaining some improved method of treatment applicable to human cases. The use of Dakin's solution in the eye was naturally contraindicated because of its too great irritating properties,

so that milder chlorinating solutions were sought for this purpose and the choice naturally fell upon the solution of dichloramine-T in chlorcosane, particularly as this substance had been recommended by various writers for the treatment of infective conditions of the eyes, such as trachoma. Our experiments showed that this solution, if applied to the eye before exposure to the gas, has a definite prophylactic action, and that when applied before and after exposure the resulting lesions are much less severe. (See Figs. 43, 44, 45, 46, 47.) In cases in which the exposure extends over a period of several hours, the administration of dichloramine-T in chlorcosane causes, naturally, no change in the intensity of the lesion. Here its after-use is indicated for its germicidal

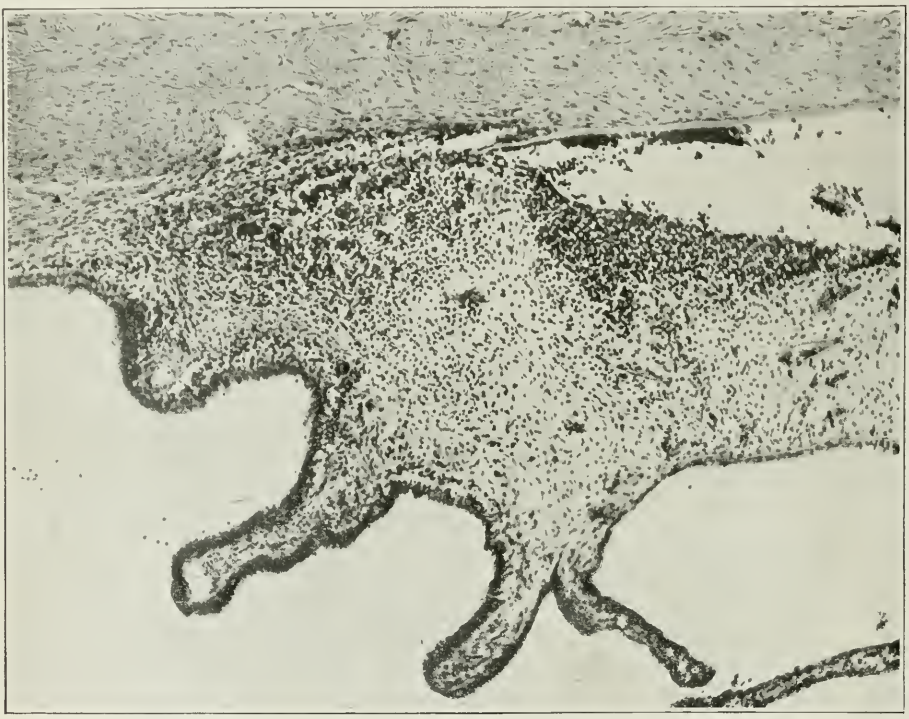

Fig. 46.—Ciliary body from eye of rabbit exposed 12 hours in gassing chamber to a concentration of 1:50,000. Animal died 92 hours later. Marked collection of polynuclear leucocytes in anterior chamber, in the ciliary body, and in the iris of the left eye which had received no treatment with the dichloramine-T solution. Same rabbit as in Fig. 44.

action, and the prevention of secondary infection. It seems to us likely that instillations of dichloramine-T in chlorcosane solutions could be used as prophylactic methods on the battlefield during a known gas attack, and that in cases of severe eye injury due to dichlorethylsulphide its use should be continued for the purpose of preventing secondary infection.

SUMMARY OF TREATMENT

1. The use of any method of treatment which brings pressure upon the lids and eyeball such as tight bandaging or heavy compresses is absolutely contraindicated.

2. For the mild cases, frequent irrigation with saturated boracic acid, the use of light weight boracic acid compresses, hot vapor baths, and protection of the eyes by darkening of the room, or by a light gauze bandage or by the use of smoked goggles are recommended.

3. Special care must be taken to prevent the gluing together of the eyelids by accumulation of the exudate. Should this occur the exudate should be softened and washed away with boracic acid with care to avoid forcible separation of the lids.

4. The use of argyrol, silvol, etc., is in our opinion, undesirable.

5. The use of cocaine is considered unwise.

6. For the severe forms the use of a 1 per cent Dakin's solution is found to be too irritating. We therefore recommend the employment of the chlorcosane

Fig. 47.—Iris of same eye as in preceding figure, showing congestion, edema and polynuclear infiltration. Marked polynuclear exudate in the anterior chamber.

of dichloramine-T in a strength of 0.5 to 1 per cent, or even stronger. We further advise that in all cases of exposure to mustard gas this solution be used as an immediate irrigant for its prophylactic effects, followed in the milder cases of injury by boracic acid irrigation and in the severe cases by repeated irrigations with the dichloramine-T solution for the prevention of secondary infection.

7. For the treatment of the refractive errors and more permanent disturbances of vision the patient must be referred to a competent ophthalmologist.

CONCLUSIONS

1. The action of mustard gas upon the cornea and conjunctiva is essentially the same as that upon the skin. The conjunctiva is, however, less susceptible to

the action, or better protected, as the degree of necrosis produced in it is always less than that in the cornea or the epidermis.

2. Exposures to dilute concentrations of the vapor produce slight degenerations of the corneal and conjunctival epithelium followed by a simple conjunctivitis. The use of a 2 per cent alkaline aqueous fluorescein solution in demonstrating the necrosis of the corneal epithelium within ten to fifteen minutes after exposure to gassing has great clinical value.

3. Exposures to stronger concentrations produce a more or less complete necrosis of the corneal vertex, extending throughout the entire depth of the cornea. Purulent exudation into the anterior chamber may occur; but no changes except congestion and edema were observed in the posterior chamber or optic nerve in noninfected cases. In severe cases iridocyclitis and iritis may occur without secondary infection. The conjunctival epithelium also suffers necrosis, and there results an intense edema of the subconjunctival tissues with marked congestion, multiple hemorrhages, leucocyte infiltration, and frequently secondary liquefaction necrosis. The depth of the necrosis in the conjunctiva is much less than that in the palpebral epidermis. This difference in degree of escharization can be explained in part by the penetration of the hair follicles on the skin surface, and in part by the moistness of the conjunctival surfaces and the lacrimation. A diffuse mild inflammation of the peribulbar tissues occurs, often with marked infiltration of the ocular muscles.

4. No metastatic lesions of the eye could be produced experimentally by applications of mustard gas to other regions of the body, or by subcutaneous or intraperitoneal injections.

5. For the milder forms of mustard gas conjunctivitis we recommend immediate irrigation with the 0.5 to 1 per cent chlorcosane solution of dichloramine-T followed by frequent irrigation with saturated boracic acid solution. For the severe forms the same initial treatment followed by frequent irrigations with the dichloramine-T alternating with boracic acid. We advise against the use of bandages or compresses bringing pressure upon the eye, against the use of colloidal silver preparations, and against the use of cocaine. During exposure to mustard gas vapor the dichloramine-T solution may be used as a prophylactic agent.

6. Healing in the more severe forms results in vascularization and cicatrization of the cornea with marked disturbances in vision. Even in the milder forms of conjunctivitis, localized roughness or irregularity in the conjunctival surface may persist for weeks as the result of localized edema, hyperemia, cellular infiltration, etc. Serious refractive errors and reduction of vision result, even in mild cases. For the correction of the disturbances of vision the patient should be referred to a competent specialist.

THE TREATMENT OF DICHLORETHYLSULPHIDE ("MUSTARD GAS") INJURIES*

Method of the University of Michigan Pathological Laboratory

By Aldred S. Warthin, Ph.D., M.D.; C. V. Weller, M.S., M.D.; Capt Lester Roos, M.D., and G. R. Herrmann, M.S., M.D.

VERY little has been published, or made available to the medical profession, of the treatment of mustard gas injuries. This can be explained, in part at least, by military exigencies, but also, without doubt, chiefly by the fact that the treatment has been largely empirical or experimental.

Mandel and *Gibson* (*Journal American Medical Association,* December 8, 1917) give a summary of the treatment used abroad at the time of their writing. This treatment consists essentially of the use of a 10 per cent sodium bicarbonate solution for the cutaneous burns, irrigation of the eyes with boric acid solution, use of alkalies internally, bleeding for the pulmonary edema, opiates for the paroxysmal cough and treatment of complications as they arise.

Teulières (*Journal de Médecine de Bordeaux*, 1917, xlvi, p. 247; 1918, xlvii, p. 37) writing of the ocular lesions produced by mustard gas says that the treatment consists of the application of warm vapor and the instillation of a collyrium of atropine and iodoform ointment. From his article it would appear that bicarbonate water is used as an eye wash as a first-aid measure to those exposed to the gas.

Teulières and *Valois* (*Archives d' Ophtalmologie*, 1916-17, xxxv, p. 403) again treat of the ocular lesions and state that the treatment that has given the best results is the eye-bath with warm vapor lasting for ten minutes and repeated from four to five times daily. They also give instillations of adrenalin and cocaine solution for the pain and frequent instillations of atropine when the iris is involved.

Giraud (*Journal de Médecine et de Chirurgie*, November 25, 1917, lxxxviii, p. 890) gives the methods used in the French army at that time, as follows: Use of bicarbonate solution at the first-aid station, both for the eyes and the skin burns, followed in the case of the latter by a dressing of Vincent's powder (boric acid and calcium hypochlorite). The lesions of the respiratory tract are given a purely symptomatic treatment of revulsions, opiates and expectorants. He mentions the fact that many men claim to have escaped the toxic action of the gas while smoking.

Pissarello (*Giornale di Medicine Militaire*, 1918, lxvii, p. 128) gives the ophthalmologic aspects of mustard gassing, and sums up the treatment as follows: Patient immediately undressed; clothing aired and sunned. Bandage removed from eye at once, if present, as it may be a cause of corneal abrasion. Bandage a danger in cases of bulbar chemosis. Use light gauze curtain be-

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fore eyes. Two per cent bicarbonate or boiled sterile water as an eye wash, with warm vapor fomentations, twenty minutes each, three times daily. Avoid bandages and cocaine. Zinc oxide ointment for the lid lesions. For the skin lesions use pomade of vaseline and 10 per cent bicarbonate of soda. Patients should be kept in a warm moist ward to prevent bronchial complications. Keep ward air moist by a boiler of 2 per cent bicarbonate solution. Use this solution as a gargle also. Dover's powder, chloral and bromide mixture, opium and

Fig. 1.—Foot 24 hours after exposure of 4 hours in shoe contaminated with mustard gas. Marked tense vesicles. Four hours after exposure, treatment by immersion in Dakin's solution was begun with immediate good results.

Fig. 2.—Photograph of foot six weeks after contamination of shoe with few drops of mustard gas. Six weeks treatment with zinc stearate, American oil, and vaseline produced the picture seen in the figure. Within one week after treatment with Dakin's solution and saline baths the lesions were entirely epithelialized, with resulting prompt and complete recovery.

belladonna may be used for cough and nervous symptoms. Pissarello observed no internal toxic action of the gas.

Bandaline and *Poliakoff (Bull. de l'Acad. de Médecine*, July 9, 1918, lxxx, p. 30) advises the use of hot-air douches (150° to 180° C.), under pressure of 300 gm.; to give relief to the intense pain and insomnia following mustard gas burns. He also advises the use of a "linoserum" (infusion of flax seed 1.5 p. 100, 1000 grm., sodium chloride pure, 9 grms. filtered and sterilized in auto-

Fig. 3.—One week after 10 to 12 minutes' exposure to strong concentration of mustard gas vapor; erythema and pigmentation of skin; acute urethritis and phimosis.

Fig. 4.—Buttocks of same patient as the preceding, taken at the same time, showing desquamation of necrotic epidermis. As in most of the mild cases, the greater severity of the lesions about the genitals and buttocks is well shown.

Fig. 5.—Genitals of same patient as the preceding, two weeks after exposure; during these two weeks he had been treated with applications of zinc stearate, vaseline and olive oil, with increasing necrosis of the epidermis. When finally persuaded to use the hip bath of Dakin's solution alternating with saline baths the effects were so prompt and so beneficial to the patient that he became one of the most enthusiastic advocates of the method. The change in the method of treatment effected prompt healing.

Fig. 6.—Photograph taken two weeks after one-half hour's exposure to strong concentration of mustard gas vapor. During this time patient was treated with zinc stearate and oily-base methods with resultant secondary infection, ulceration and gangrene of the skin of the parts. This patient had tried so many ointments and applications that he was with difficulty persuaded to try the Dakin's and saline hip bath method. On beginning this method of treatment the beneficial effects were so marked that he also became an enthusiastic advocate of the method. Progress of healing from the time of change of treatment uninterrupted.

clave, 20 minutes at 120° C.) to prevent dressings adhering to wound surfaces.

The clinical resemblance of mustard gas lesions of the skin to thermal burns has led naturally to the use of alkalies externally and to the application of air-excluding protectives, such as oils, pastes, ointments, pomades, paraffin, oiled paper, dusting powders, etc. The extensive use abroad of a 10 per cent bicarbonate solution is the result no doubt of its employment in the treatment of other forms of gassing.

Fig. 7.—Genitals two weeks after exposure to mustard gas vapor, during this time treatment was of the ordinary grease method and resulted in secondary infection, deep necrosis and phimosis. This photograph shows especially well the deep follicular abscesses in the skin of the scrotum and penis.

Fig. 8.—Genitals twelve days after three-quarters of an hour exposure to strong concentration of mustard gas. During this time treatment with zinc stearate, etc. Stinking gangrene of the skin of the scrotum and penis. These parts were covered with a tough greenish yellow necrotic membrane, forming a complete cast of the parts and holding the infection and pus beneath it. This membrane had to be removed to permit access of the Dakin's and saline solutions. The condition shown is a very striking example of the bad effects of the grease method of treatment.

From the laboratory standpoint and theoretically it became very evident to us that any form of treatment covering the surface of the injured skin areas and forming an air-excluding and germ-including coating was the worst

possible method of treatment. Our animal experiments with zinc stearate and other forms of oily coatings confirmed this view. Inasmuch as mustard gas causes a necrosis, more or less deep, of the skin, cornea and conjunctiva, and mucous membrane of the respiratory tract, the therapeutic problems are as follows:

1. To sterilize the dead tissue and prevent infection of the eschar.
2. To prevent further necrosis by removing pressure.
3. To promote removal of the eschar and rapid regeneration and healing without secondary infections.

Naturally, the use of Dakin's solution suggested itself as an ideal method

Fig. 9.—Method of applying Dakin's and saline solutions to mustard gas lesions of the genitals. Genitals of this patient shown in Fig. 6.

particularly, because the use of a chlorinating solution would also serve to destroy any mustard gas remaining in the skin, hair follicles, or sweat glands. The use of the bath method, as carried out in the treatment of severe thermal burns and necrotic and suppurative conditions of the skin, and especially, because of the danger of bedsores and secondary necrosis from pressure, seemed an ideal method of treating severe mustard gas lesions.

An opportunity of applying these principles to the treatment of mustard gas lesions in human beings presented itself. A number of cases with mustard gas injuries varying from the mildest form up to the most severe and fatal degree were seen by us. When first seen they had been treated for a week by

the air-excluding method of zinc stearate, olive oil, mineral oil, oiled paper, etc. The severe cases were all infected, stinking with the odor of gangrene; the injured areas of the skin were gangrenous and dripping with a purulent sanguineous fluid, and large areas of pressure decubitus were developing. An opportunity was afforded for the practical working of our suggestions; and the

Fig. 10.—Diffuse erythema of the skin due to ten to twelve minutes exposure to strong concentration of mustard gas. Treated one week by the grease method with increasing infection of the dead skin, particularly around the genitals and anus. Change of treatment of the wet Dakin and saline methods resulted in prompt healing.

results justified this method of treatment, although, under the crude and inefficient conditions obtaining, the complete immersion method was not given a complete trial. For local lesions, as of the genitals, the hip bath proved the efficacy of this method.

We, therefore, believe that the method of treatment outlined below is of great practical value. It is founded upon the pathology of the lesions produced by mustard gas, and is based upon scientific principles. It is not empirical or symptomatic. In practice it has produced good results.

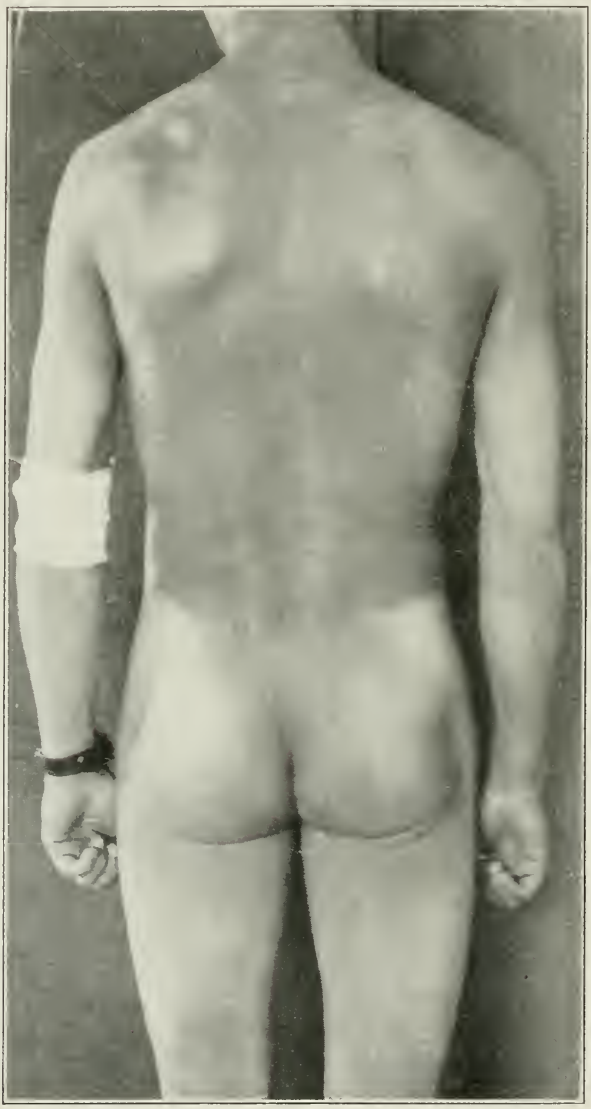

Fig. 11. Rear view of same patient shown in Fig. 10.

THE TREATMENT OF DICHLORETHYLSULPHIDE INJURIES

A. Mild Injuries.—Wash immediately, or better, immerse parts one-half to two hours in Dakin's solution (strength of about 0.5 per cent hypochlorous acid). If too irritating, and when the skin is unbroken this is not likely to be the case, dilute the solution or shorten time of immersion. If injured surfaces

are very large use full bath; for lesions of the genital region use sitz bath. When immersion of parts is not expedient use wet Dakin's dressings or irrigate with Dakin's solution. If the wet treatment (which we consider by far the best) can not be carried out, the application of dichloramine-T in chlorcosane or chloramine-T in sodium stearate may be used. These procedures will serve

Fig. 12.—Photograph taken one week after 40 minutes' exposure to strong [illegible] mustard gas vapor. Treated with grease method during this time with increasing infection and sloughing of epidermis. Change of treatment to the wet Dakin's and saline method effected [illegible]

a double purpose of chlorinating and rendering inactive any dichlorethylsulphide remaining in the skin, hair follicles, etc., and also disinfecting the damaged skin surface. This primary disinfection of the skin is of very great im-

portance in the prevention of the secondary infections that are so often of a serious character. After the Dakin's solution, use wet dressings, irrigation or bath of sterile hypertonic saline (5 to 10 per cent), alternating with the above Dakin's solution and a sterile physiologic saline, according to judgment, about as follows: Dakin's 1 to 2 hours, hypertonic saline 2 hours, physiologic saline 1 hour, and then repeat until lesions appear and extent of injury can be determined. As long as the lesion remains an erythema continue this treatment during the daytime. At night, dry the skin under aseptic precautions, and apply a vanishing surgical cream containing hypochlorous acid or liberating chlorine, of the type of the chlorazene (chloramine-T, 1 per cent, in sodium stearate) surgical cream, or instead, use wet hypertonic saline dressings. Dusting powders are inadvisable because of crusting and possibility of infection. Chloramine-T and dichloramine-T in full strength powder form are too irritating. We have had no experience with Vincent's powder but on general principles

Fig. 13.—Photograph one week after one-half hour exposure to strong concentration of mustard gas. During this time treated by the grease method. Photograph shows very well the protection afforded by the tight belt. The more marked lesions in the axillae, bends of the elbows, and genitals and the large flaky character of the primary desquamation and the pigmentation are well shown.

would not favor its use. We also advise against the use of silver nitrate, iodine, potassium permanganate, or other local applications. Saturated magnesium sulphate solution proved irritating and no benefits were observed from its use.

In the case of vesicle formation, empty vesicles early under aseptic precautions, by means of a hypodermic syringe or sterile needle with slight pressure upon the vesicle, and allow intact vesicle wall to collapse and seal down upon its base. After this procedure continue with alternating Dakin's and sterile salines, as above. If vesicles are not drained early, the fluid content may, within 4 to 5 hours, coagulate to such an extent that a large coagulum is formed that can not be removed, and forms a possible medium for bacterial growth. It is very important that skin damaged by mustard gas be protected from trauma. Slight injuries, even ordinary pressures of the body, will cause the development of secondary vesicles or decubitus in the injured areas.

The use of unguents and ointments with oily bases, such as zinc stearate, olive oil, oleum petrolatum, or any form of crude vaseline or other protecting oil, or such air-excluding and infection-including protectives as oiled paper, paraffin sprays and coatings, such as are employed in the treatment of thermal burns, is strongly condemned by us in the treatment of dichlorethylsulphide

Fig. 14.—Back of same patient as the preceding figure.

injuries. The principle of excluding the air for the purpose of lessening pain in the treatment of thermal burns is not applicable here because of the relative anesthesia of the dichlorethylsulphide lesions in their earlier stages. Exceptions to the above rule are the sodium stearate impregnated with chloramine-T and the chlorcosane solution of dichloramine-T, as in these cases there is an active and persistent germicidal agent present. In the case of denuded surfaces with

much pain and when bedsores have developed, the colloidal saline bath is strongly advocated by us. This bath is made as follows: Dissolve one pound of commercial cornstarch and one pound of sodium bicarbonate in 20 to 30 gallons of sterile physiologic salt solution, at a temperature of 90° to 95°. The patient can be left immersed in this, when necessary, from 15 minutes to 48 hours. The patient should be constantly watched by the nurse. Should pulse become weak, give strychnin or digipuratum or any other active digitalis preparation, or remove from bath, and apply blankets and heat.

Mild Conjunctivitis.—Avoid pressure from heavy compresses or tight bandages. Cold compresses of saturated boric acid constantly applied without pressure for 12 to 24 hours or longer, or hot vapor eye baths relieve the pain and discomfort, particularly the feeling of "sand in the eyes," and reduce the congestion. Personal experience leads us to recommend highly the use of a 0.5 per cent solution of dichloramine-T in chlorcosane both as a prophylactic and therapeutic measure for the ocular conditions.

Mild Respiratory Lesions.—For the mouth and throat conditions a weak

Fig. 15.—Photograph one week after three-quarters hour exposure to strong concentration of mustard gas. Treated twelve days with grease method with resulting severe gangrene of the epidermis and large decubitus from which he died three weeks later.

Dakin's or a .25 to .50 per cent chlorazene solution. For the aphonia use ice bag externally, and steam inhalations, with or without compound tincture of benzoin.

B. Severe Injuries.—When necrosis of the skin, more or less extensive develops, follow the same line of treatment given above: full bath, irrigation, slush or sponge bath, or wet packs of Dakin's solution, alternating with physiologic and hypertonic salines, or the colloidal bicarbonate bath should be constantly employed. When the severe lesions are upon the shoulders, buttocks, etc., the greatest care must be taken to avoid bedsores, as they will develop very quickly. For this purpose the constant colloidal or saline bath, with patient hung in canvas body cradle to take off pressure should be used. The cradle also gives increased facility in handling. It is of the greatest importance to protect the damaged areas from secondary trauma.

Where decubitus or sloughs occur the necrotic layer should be removed,

either with sterile forceps or by means of frequent hot irrigations under pressure. For this purpose saline, Dakin's, 1:10,000 potassium permanganate solution, etc., should be used. If the necrotic areas have become infected through neglect or improper treatment, the use of Dakin's or a similar solution should be pushed, alternating with hypertonic saline baths. A hyperchlorous solution made according to Carrel's method can be applied here with good results:

Fig. 16.—Photograph one week after three-quarters hour exposure to strong concentration of mustard gas. Treated by the grease method with resultant diffuse infection and gangrene of the skin of the back. Change to the wet Dakin's and saline methods removed the odor of gangrene at once, checked the infection and promoted prompt repair.

To one liter of water add 12.5 grams of bleaching powder, shake vigorously, then add 12.5 grams of boric acid powder, and shake again. Allow the mixture to stand for some hours, preferably overnight, then filter off, when the clear solution is ready for use. This solution contains about .54 per cent of hypochlorous acid, 1.28 per cent calcium biborate and .17 per cent calcium

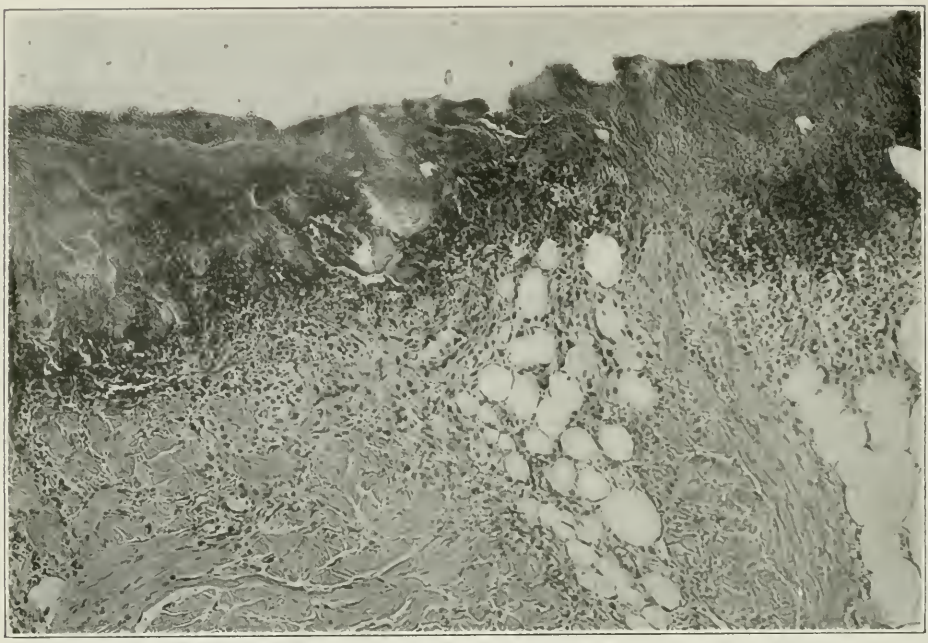

Fig. 17.—Microscopic appearance of mustard gas decubitus four weeks after exposure.

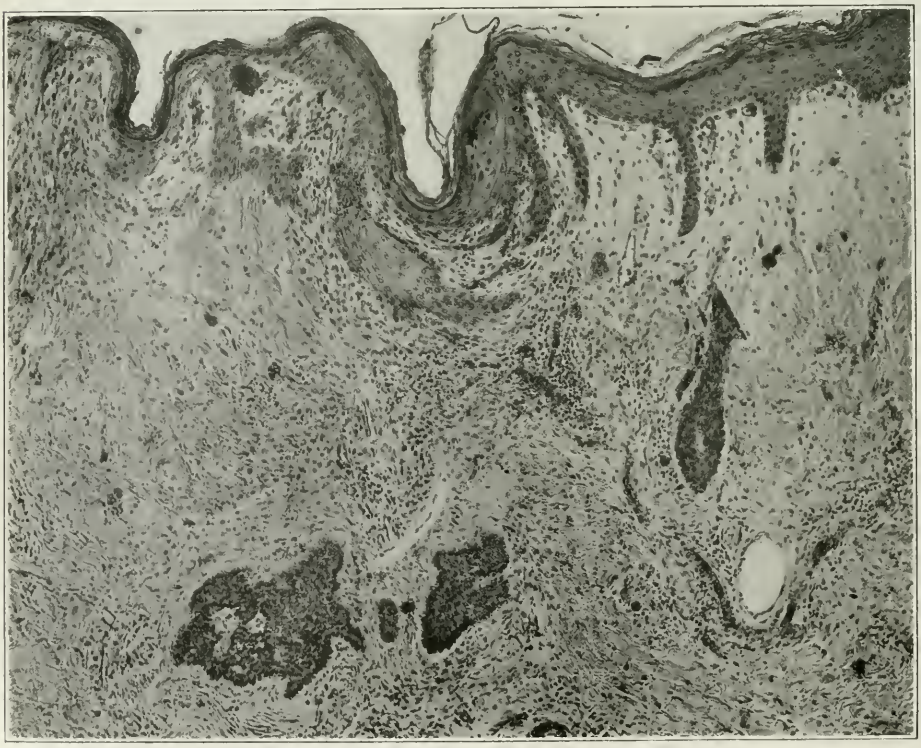

Fig. 18.—Photomicrograph of regenerating epidermis under the wet Dakin's and saline method of treatment four weeks after the injury. Note the regeneration of the epithelium from the remains of the hair follicles and sweat glands.

chloride. This is about the most practical concentration of hypochlorous acid, as stronger solutions rapidly lose strength.

When the patients are very weak, temperature rising, and infection progressing it may be advisable to employ tepid sponge baths of above solutions.

COMPLICATIONS.—*Shock* may develop immediately after the exposure but is usually not as severe as in thermal burns. Treat as in surgical shock.

Kidney.—From the time of exposure fluids should be forced to dilute the urine and lessen renal damage. When there is severe shock and excessive vomiting use Murphy drip. Use a low protein salt-free diet. When a hypertonic bath or irrigation is used great care must be taken to keep up the intake of

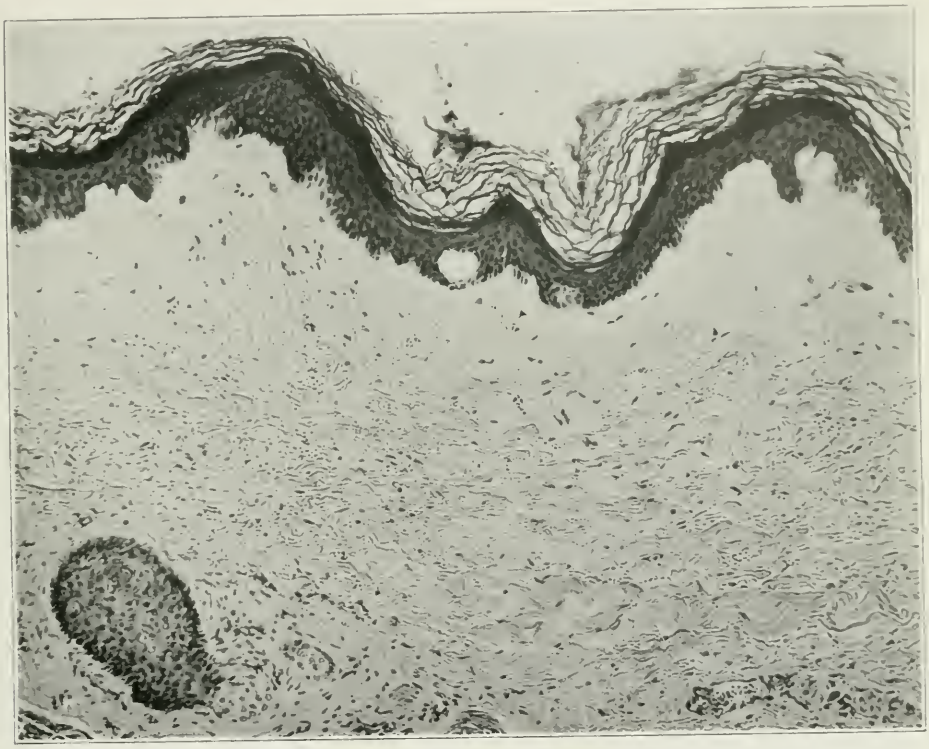

Fig. 19.—Completely healed mustard gas lesion four weeks after injury, treated twelve days with grease method with increasing infection and gangrene. Under the wet Dakin's and saline method, infection was checked promptly and healing begun.

water and prevent concentration of urine. Sodium bicarbonate may be given internally. The strengthening of the cardiac function increases the urinary output. The use of digipuratum is apparently of value here, according to our experience with human cases.

Heart.—The heart rate is usually 120-140, and there is some ventricular dilatation, probably with little or no myocardial degeneration (as shown by autopsy). The use of active digitalis compounds is here indicated. Digipuratum in doses of 1.5 grams 3 to 4 times daily seemed of benefit in our cases.

Lungs.—For the primary bronchial and pulmonary lesions there is no specific treatment. For the secondary pneumonias (infective) proceed accord-

ing to the type of infecting organism, which is likely to be the streptococcus.

Gastrointestinal.—Use liquid low protein diet. Sodium bicarbonate as indicated.

Furunculosis.—In the majority of severe dichlorethylsulphide injuries there develops about the second or third week a more or less widespread, often generalized furunculosis, usually beginning deep in the necrotic hair-follicles, and due to a staphylococcus pyogenes aureus infection. The furuncles range in size from miliary pustules to large painful boils. The large ones should be opened and drained, and a stock staphylococcus vaccine, or, if possible, an autogenous vaccine, should be given in large doses, 1 billion every third day for four injections.

Severe Eye Injuries.—Experimental evidence seems to indicate that the use of 5 per cent solution of dichloramine-T in chlorcosane lessens the injuries to cornea and conjunctiva, and prevents secondary infection. The use of atropine is indicated in case of involvement of the iris. The development of a chronic conjunctivitis should be prevented by the wearing of tight-fitting (but without pressure upon eyelids), antidimming goggles. The increase in refractive error or reduction of vision shown in many of the chronic irritated eyes did not respond to any treatment employed. The patient should be referred to a competent ophthalmologist for appropriate examinations and treatment for these conditions.

In the treatment of the eye lesions the use of argyrol, silver and other silver preparations, as well as cocaine, is considered unwise. (See article on Ocular Lesions, this JOURNAL, p. 785.)

General Toxic Action.—No evidences of a toxic action upon the internal organs have been seen in any of the lesions of mustard gas produced by direct application or by exposure to its vapor. Clinical studies, as far as carried out, show increased blood urea, decreased urea- and chloride-output, decreased quantitative urinary output, and increased specific gravity, with increased acidity. The toxic symptoms observed could be explained as the result of the skin destruction, damage to the respiratory tract, secondary infection, decubitus, with resulting absorption, etc. In the earlier stages symptoms of severe shock may be present. Treatment of these conditions should be carried out according to general principles.

STUDIES ON CHOLESTEROL*

V. The Blood Cholesterol in Malignant Disease and the Effect of Radium on the Blood Cholesterol.

By Georgine Luden, M.D., Rochester, Minn.

IT is universally conceded that the life of every cell in the body depends on its blood supply. It has repeatedly been demonstrated that malignant cells are aberrant though lineal descendants of normal cells[19, 42-54, 68, 69] and it would seem a foregone conclusion that cells, like individuals, must be influenced by the conditions under which they exist. Yet, strange as it may seem, little attention has been paid to the fact that the chemical composition of the blood must affect the cells as vitally as does their blood supply.

Compared with the immense amount of work that has been done on cancer from the cellular point of view, the attention given to the chemical composition of the blood in cancer has been woefully small.[71] Blood.[13, 20, 58, 59, 61, 65] Serum.[12, 18, 32, 64, 66] Nevertheless the observations of Benedict and Lewis[4] on the increase of the blood sugar content in carcinoma, Menten's[55] report on the increased alkalinity of the blood and Bloor's[5-8] work on the blood lipoids must be looked upon as landmarks in the study of malignant disease. I am convinced that physiologic chemistry will not only explain the causation, but, eventually, find the cure for cancer.

In no field of cancer research has the chemical composition of the blood received less attention than in radium therapy. The effect of radium seems to have been studied entirely from the cellular point of view.[56, 57, 70, 14] In Colwell and Russ' recent monograph, for instance, data are given on the cytology of the blood following radium treatment, but the chemical composition of the blood is not even mentioned, although a whole chapter is devoted to the chemical action of radium on various substances.

Robertson and Burnett's[60] publication on the rapid growth of tumor transplants in rats following intravenous injections of cholesterol, first called my attention to the cholesterol content of the blood and its possible relation to malignant disease.[38] The idea that cholesterol might in some way promote cell-proliferation seemed to be supported by the increase of the blood cholesterol in pregnancy and its return to normal after delivery,[1, 2, 3, 10, 63, 64] as well as by Browder's report on the increased rate of division in paramecium when cholesterol is added to the culture medium.

Between November, 1915, and December, 1917, I tested 1,069 samples for cholesterol. This number included 1,052 determinations of blood cholesterol (human, goat, gopher, and dog's blood), 14 determinations on foodstuffs and

*From the Mayo Foundation, Rochester, Minn.

*Presented before the Joint Session of the Federation of American Societies of Experimental Biology, Rochester, Minnesota, December, 1917.

3 on human pus. Of 743 blood samples parallel determinations in triplicate were made with Bloor's original method (Bloor I with sodium ethylate) and with its modification (Bloor II without sodium ethylate),[5,6] making a total of 4,658 determinations with Bloor's methods. The advantage of these parallel determinations, by which the amount of cholesterol split products present in the blood is revealed, was shown by 2,196 tests made on pathologic human blood, including 70 miscellaneous conditions, 41 cases of pernicious anemia, 37 of exophthalmic goiter, 3 of myxedema tested 18 times at various intervals during the administration of the thyroid hormone (Kendall's thyroxin), 79 determinations on my own blood as normal controls and during experimental

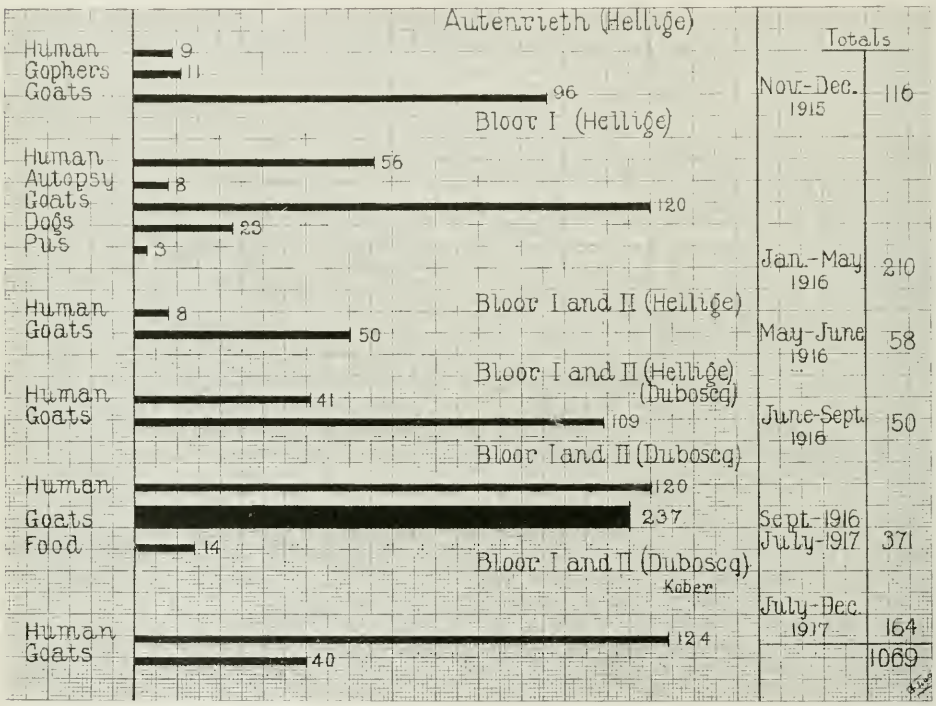

Fig. 1.—*Cholesterol determinations made by the writer from November,* 1915, *to December,* 1917. Methods used: Autenrieth-Funk, Bloor I, II. Bloor I, II indicates parallel determinations with both methods. Colorimeters: Hellige, Hellige-Dubosc, Dubosc-Kober. Hyphenated designation of two colorimeters indicates parallel determinations with both instruments. Samples used in determinations are given in margin; human blood, goat's blood, human pus, etc. Fourth entry from the bottom has been drawn in double width on account of the number of determinations made; goat's blood 237.

diets,[41] 9 cases of sarcoma (16 determinations) and 92 determinations on the blood cholesterol in carcinoma before and after radium treatment including 20 weekly determinations on one patient (Figs. 1 and 2). The technic used in my determinations has been published previously.[37, 41]

Two points should be mentioned in connection with the technic: First, the two types found in human blood (Figs. 3 and 4), to which I called attention in my second study on cholesterol,[39] and which have since also been observed by Bloor,[8] and second, the value of parallel determinations with the Bloor I and Bloor II methods.[40]

Advantage of Parallel Determinations with Bloor I and II Methods.—Lifschütz[33-37] has shown that certain bile salts and bile acids are cholesterol split-products. These bile derivatives are eliminated in the Bloor I method by the use of sodium ethylate. In the Bloor II method no sodium ethylate is used and the tests contain both cholesterol and bile derivatives. The difference between the Bloor I and Bloor II tests, therefore, represents the amount of bile derivatives[10] present in the blood sample. An absence of difference between the two tests, or equal values by the Bloor I and Bloor II methods, indicates some inability on the part of the organism to oxidize its blood cholesterol to bile derivatives, in other words, some disturbance of cholesterol metabolism. In normal blood, there is always a difference between the Bloor I and Bloor II values, but in carcinoma this difference is absent in a high per-

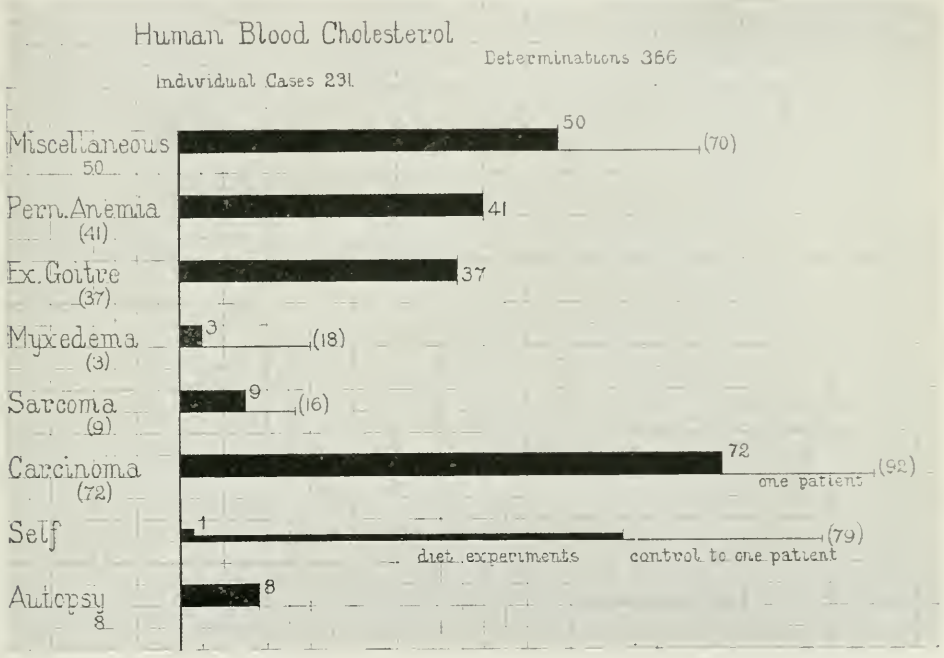

Fig. 2.—*Human blood, cholesterol determinations under various conditions.* Wide bar denotes number of determinations made on individual cases. Narrow bar and number in brackets denotes additional determinations on the same person. Necropsy: blood taken at necropsy at different number of hours after death, to study effect of postmortem changes. Cholesterol values were unchanged.

centage of cases (53-56 per cent in our determinations) and we find equal values with both tests. In a series of 252 determinations in nonmalignant cases I have not observed equal values; however, this does not signify that equal values are to be looked upon as unmistakable diagnostic evidence. The test for cholesterol in the blood is a clinical test capable of giving valuable information but it is not, unfortunately, as so often has been thought, a diagnostic test. It is not expected that the test for albumen in the urine, or the hemoglobin test should furnish a conclusive differential diagnosis, nor should any such evidence be expected from the blood cholesterol test. The unwarranted assumption that blood cholesterol determinations should settle diagnoses has

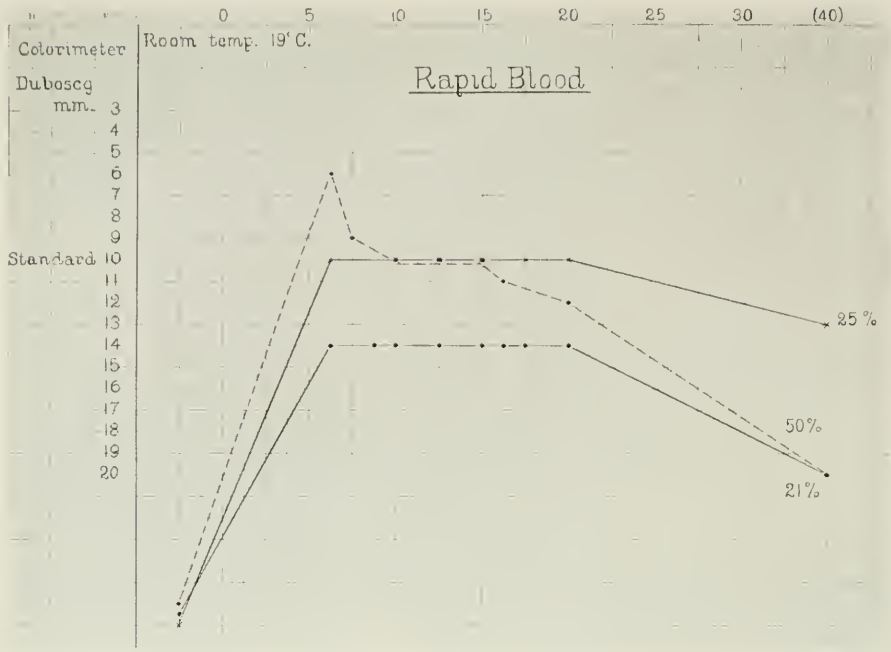

Fig. 3.—*Types of reaction in cholesterol determinations on human blood.* Rapid blood ripens more quickly than cholesterol standard test.

X-X-X-: Cholesterol standard test.

. — . . — . Bloor I test.

– – – . – – – . Bloor II test.

Numbers in margin denote mm. on Duboscq colorimeter. Percentage of loss of original maximum color value in 40 minutes indicated at the end of each curve.

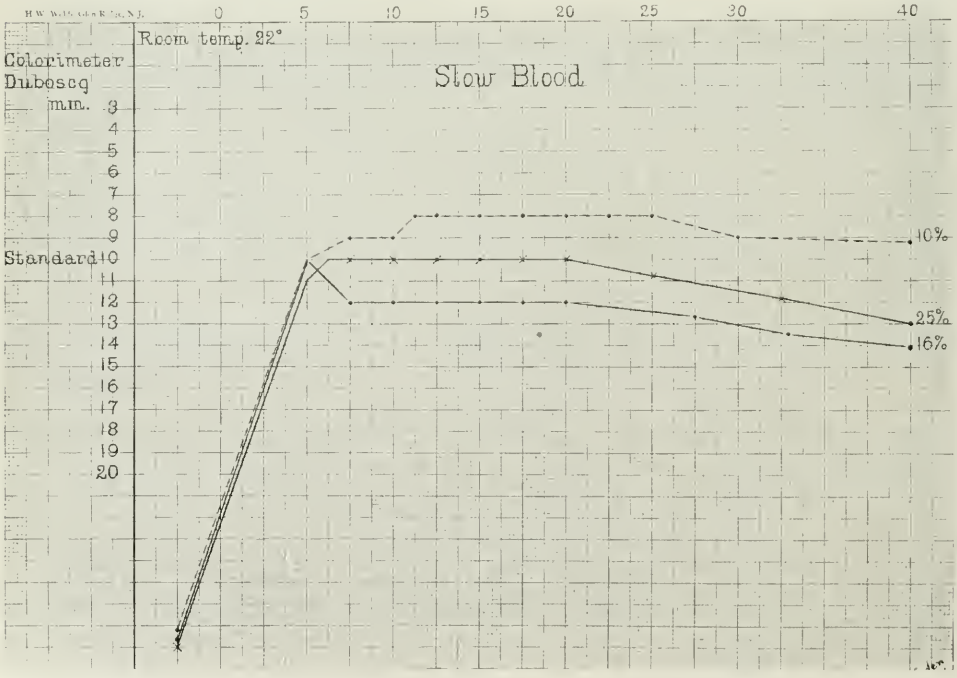

Fig. 4.—Slow blood ripens more slowly than cholesterol standard test. (Explanatory notes the same as for Fig. 3.)

done much to discredit the value of such determinations in the eyes of clinicians, and valuable information concerning metabolic problems must have been lost in consequence.

Cholesterol Values Found in Human Blood.—In my previous publications[39, 40, 41] the values reported have been based on the amount of cholesterol in milligrams found in each determination or test, that is, in 6 c.c. of the chloroform extract representing 0.3 c.c. of whole blood. The foregoing values might, therefore, be designated as "test values." Since a uniform terminology based on mg. per 100 c.c. has been adopted for determinations of other blood constituents, blood urea and blood sugar, as well as for blood cholesterol, and

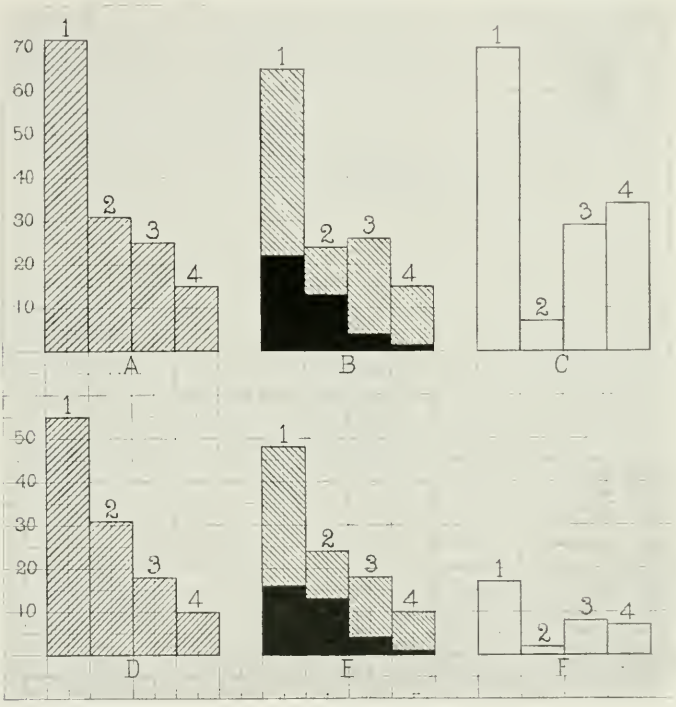

Fig. 5.—*Blood cholesterol values given in numbers of cases.*

1. Total number of cases.
2. Total number of cases with high values.
3. Total number of cases with increased values.
4. Total number of cases with normal values.
▬ = Equal values.

A. Relation of high, increased and normal values in all the determinations on carcinoma (various methods).

B. Relation of high, increased and normal values in determinations on carcinoma with Bloor I and Bloor II methods. Note preponderance of high equal values in B. 2.

C. Miscellaneous, nonmalignant cases, no equal values (Bloor I, II).

D. Relation of high, increased, and normal values in all the determinations on carcinoma before radium treatment (various methods).

E. Relation of high, increased, and normal values in carcinoma cases tested (Bloor I and II) before radium treatment. Note relative increase of both high and equal values.

F. Relation of high, increased, and normal values in carcinoma after radium treatment (tested with Bloor I, II). Observe the disappearance of the equal values and the great relative decrease of high values, which makes this diagram similar to diagram C.

as it is highly desirable that a standardized procedure for blood cholesterol determinations should be adopted by all workers in this field of blood chemistry, the values found in our determinations will in future be expressed in milli-

grams per 100 c.c. only. The test values referred to may be converted into milligrams per 100 c.c. of whole blood by simply dividing by 3, the values given in my previous publications. The Bloor I method will remain the basis of comparison as has been the case in previous publications. The Bloor II values show much greater fluctuations even in the blood of the same individual taken at different times, and the factors that cause these fluctuations are not all fully explained, since the fluctuations themselves depend on the rate of cholesterol metabolism.

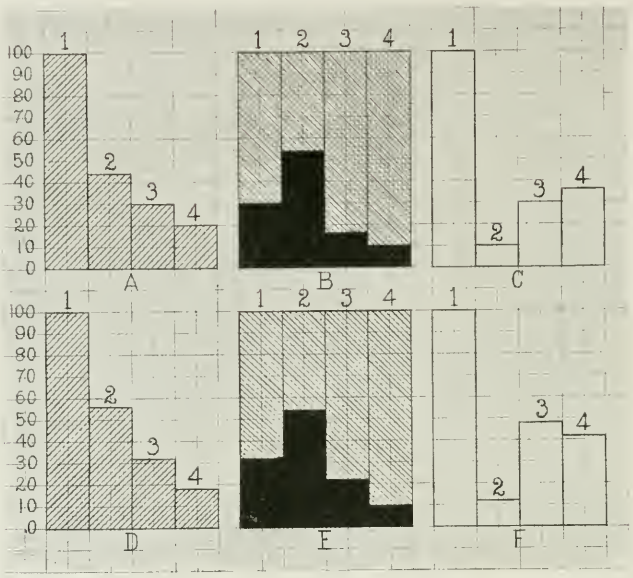

Fig. 6.—*Relation of high, increased and normal blood cholesterol values.* (Given in percentage of cases.)

1. Total of determinations in percentage of cases.
2. High values in percentage of cases.
3. Increased values in percentage of cases.
4. Normal values in percentage of cases. Equal values in percentage of cases.

A. Relation of values in all the carcinoma cases (various methods of extraction).

B. Percentage of equal values. Observe preponderance of 2 (high values) (Bloor I, II).

C. Miscellaneous, nonmalignant cases; no equal values (Bloor I, II).

D. Relation of values in carcinoma before radium treatment (Bloor I, II).

E. Percentage of equal values in carcinoma before radium treatment (Bloor I, II). Observe preponderance of high, equal values.

F. Relation of values in carcinoma after radium treatment. Observe disappearance of equal values and the striking reduction of high values which cause this diagram to resemble diagram C.

BLOOD CHOLESTEROL VALUES WITH THE BLOOR I METHOD: MILLIGRAM OF CHOLESTEROL PER 100 C.C. OF WHOLE BLOOD

1. Normal values 70-100 mg. found in healthy persons on mixed diet, digestion being duly excluded, in exophthalmic goiter and in some cases of sarcoma.

2. Increased values 100-140 mg. found during the process of digestion and in various more or less pathologic conditions.

3. High values 140-200 mg. found associated with pathologic conditions only.

4. Unusual values over 200 mg. found in cases of myxedema, and in some cases of carcinoma.

This classification of values is based on over 2,000 determinations; it

was adopted for practical purposes only, and represents the values I have observed, but should not be looked on as a diagnostic classification, since the cholesterol test does not furnish conclusive diagnostic evidence. That higher values have been reported as normal must be accounted for by the methods and the technic by which those values were obtained, such, for example, as leaving the tests in the dark for fifteen minutes at a relatively high temperature[39, 40] and by the two types of reaction found in human blood. It is obvious that if a sample of "slow" blood is tested against a "fading" standard, the values obtained must be relatively higher.

Blood Cholesterol Values in Patients Suffering from Carcinoma.—High values are generally found in cases of carcinoma: they were found in 43 per cent of all our cancer patients and in 56 per cent of those who were to have radium treatment. I am at a loss to understand how Denis[17] came to the conclusion that I had reported low values in connection with cancer cachexia, as this condition is not even mentioned in the article to which they refer. Several of our patients, moreover, with high values showed distinct symptoms of cachexia. But as the technic used in cholesterol determinations controls the values to a considerable extent, a uniform technic alone can assure comparable values.

For the sake of comparison with patients suffering from carcinoma, a group of 70 patients suffering with various nonmalignant conditions, such as tonsillitis, gastric disturbances, biliary disturbances, skin diseases, malaria, etc., was tabulated similarly to the 72 cancer cases. No equal values were found in

TABLE I

CHOLESTEROL VALUES IN CARCINOMA (CASES DIAGNOSED CLINICALLY AND MICROSCOPICALLY AND CLINICALLY ONLY)

CASES	72	CASES TESTED WITH BLOOD I AND II—65		EQUAL VALUES 65 CASES	22 (34%)
High values	31 (43%)	High values	24 (37%)	24 cases	13 (54%)
Increased "	26 (36%)	Increased "	26 (40%)	26 "	4 (15%)
Normal "	15 (20%)	Normal "	15 (23%)	15 "	1 (6.6%)

TABLE II

CARCINOMA CASES BEFORE RADIUM TREATMENT

CASES	55	CASES TESTED WITH BLOOD I AND II—48		EQUAL VALUES 48 CASES	16 (33%)
High values	31 (56%)	High values	24 (50%)	24 cases	13 (54%)
Increased "	14 (25%)	Increased "	14 (29%)	14 "	4 (28%)
Normal "	10 (18%)	Normal "	10 (20%)	10 "	1 (10%)

TABLE III

MISCELLANEOUS CASES, PATHOLOGIC BUT NONMALIGNANT

CASES	70	CASES TESTED WITH BLOOD I AND II—70		EQUAL VALUES 0
High values	7 (10%)	High values	7 (10%)	0
Increased "	29 (41%)	Increased "	29 (41%)	0
Normal "	34 (49%)	Normal "	34 (49%)	0

this group and high values occurred in only 10 per cent, increased and normal values being found in 41 and 48 per cent respectively.

Reduction of the Bloor I Values and Increase of the Bloor II Values Under Radium Treatment.—The influence of radium treatment on the blood cholesterol values is clearly shown by a group of 17 patients whose blood was tested before and after radium treatment. In this group there is a marked change in the relation of high, increased and normal values. Whereas high values preponderate in cases of carcinoma before radium treatment, the percentage of high values is lowest of all in this group and the equal values have completely disappeared. (Figs. 5 and 6.)

TABLE IV

CARCINOMA CASES AFTER RADIUM TREATMENT

CASES	17	EQUAL VALUES 0
High values	2 (11%)	0
Increased "	8 (47%)	0
Normal "	7 (41%)	0

All of these cases were tested with the Bloor I and Bloor II methods.

That the drop of the Bloor I values is accompanied by an increase of the Bloor II values resulting in an increased difference between the values found by Bloor's two methods, is graphically illustrated by Figs. 7 and 8. Since, as has been previously pointed out, this difference is due to bile derivatives, which must be looked on as oxidized or changed cholesterol,[40] it is obvious that radium treatment in some way accelerates the rate of cholesterol metabolism. Although the process by which these metabolic changes are brought about are by no means fully explained, the fact remains that the chemical composition of the blood is changed by radium treatment and it seems probable that the beneficial effect of radium in cases of malignancy may be largely due to this fact. In sarcoma the blood cholesterol values appear to be lower on the whole than in carcinoma, but equal values were found in 2 of our 9 cases (22 per cent) and the effect of radium on the blood cholesterol is identical; namely, a reduction of the Bloor I values and an increased difference between the Bloor I and Bloor II tests (Figs. 7 and 8).

That the high blood cholesterol values observed in cases of carcinoma before radium treatment can not be due merely to cell destruction, as is commonly believed, may be deduced from the following facts:

1. The cytolytic action of radium is generally conceded,[11, 14, 56, 57, 70] yet radium treatment reduces the blood cholesterol (Bloor I), as has been shown, instead of increasing it.

2. In pregnancy cell production far outweighs cell destruction, but the blood cholesterol of the mother returns to normal shortly after delivery,[1, 2, 3, 10, 63, 67] although the postpartum involution of the uterus is accompanied by a considerable amount of cell destruction and reabsorption.

3. In an egg during the process of hatching, cell destruction can not be

said to play a prominent part, but the high cholesterol content of the yolk is used by the chick embryo for the multiplication of its cells.[15]

4. In myxedema, the disease par excellence of torpid metabolism, cell destruction must be very small, yet the blood cholesterol values in myxedema are unusually high.

5. In exophthalmic goiter (I have tested 35 cases) the blood cholesterol values are well within normal range, even when basal metabolism is well nigh 100 per cent above normal (Fig. 9).

6. Cell destruction might be expected to accompany increased, rather than sluggish, metabolism yet the administration of the thyroid hormone (thyroxin), which raises the basal metabolism from subnormal to normal and above normal, simultaneously reduces the unusually high cholesterol values in myxedema to their normal level* (Figs. 10 and 11). The metabolic rate, therefore, and not

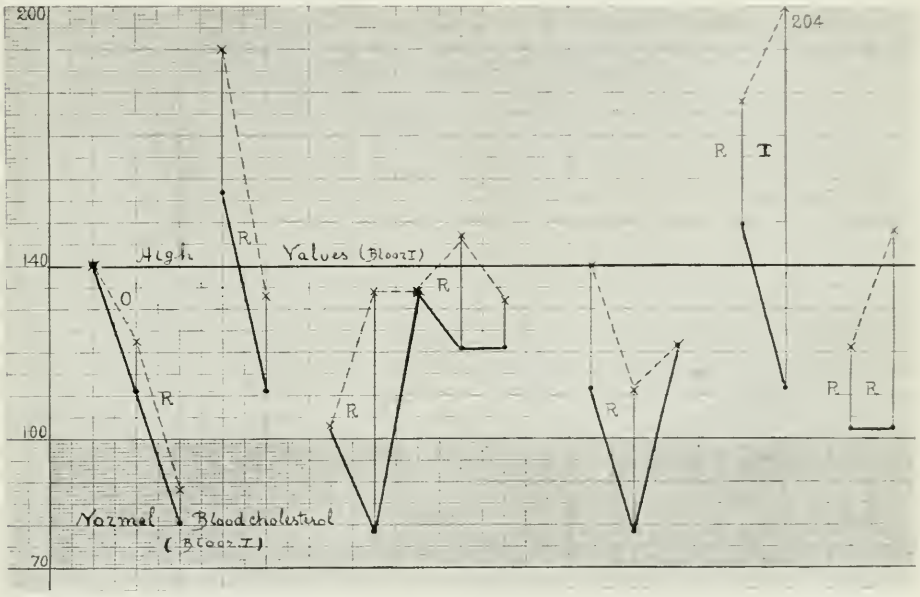

Fig. 7.—*Curve showing drop of Bloor I values and increase of Bloor II values in carcinoma after radium treatment.* (6 cases.)

—.—. Bloor I test.

– – –. – –. Bloor II test.

R - radium treatment.

T - 6 mg. of thyroxin.

In Case 1 the difference between Bloor I and II is not greatly increased even after radium treatment. The patient has since died. Case 2, marked difference even before radium treatment. Complete cure. Cases 3, 4, 5, and 6 doing well; in Case 4 the presence of carcinoma suggested by the equal values was confirmed by excision and microscopic findings (Lupus erythematosus going over into carcinoma). In Case 6, 6 mg. of thyroxin was given at patient's request. Patient left for South Africa.

mere cell destruction would seem responsible for the high blood cholesterol values that are commonly found in carcinoma.

Aside from the effect of radium on metabolic processes and thereby indirectly on the chemical composition of the blood, the following considerations may help to account for the reduction of the blood cholesterol (Bloor I) following radium treatment. Schulze and Winterstein[62] have shown that choles-

*In the writer's own blood the Bloor I cholesterol values were also found to drop whenever experimental doses of thyroxin were taken. Further experiments are in progress.

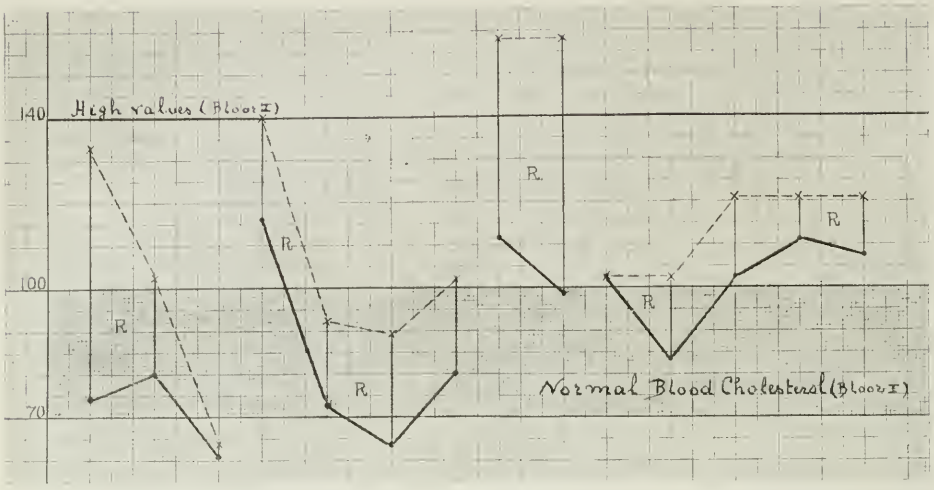

Fig. 8.—*Curve showing effect of radium treatment in sarcoma.* (4 cases.) Note that the values are lower on the whole than in carcinoma and note the reduction of the Bloor I with parallel increase of the Bloor II values, and the disappearance of the equal values after radium treatment in Case 4. Radium treatment.

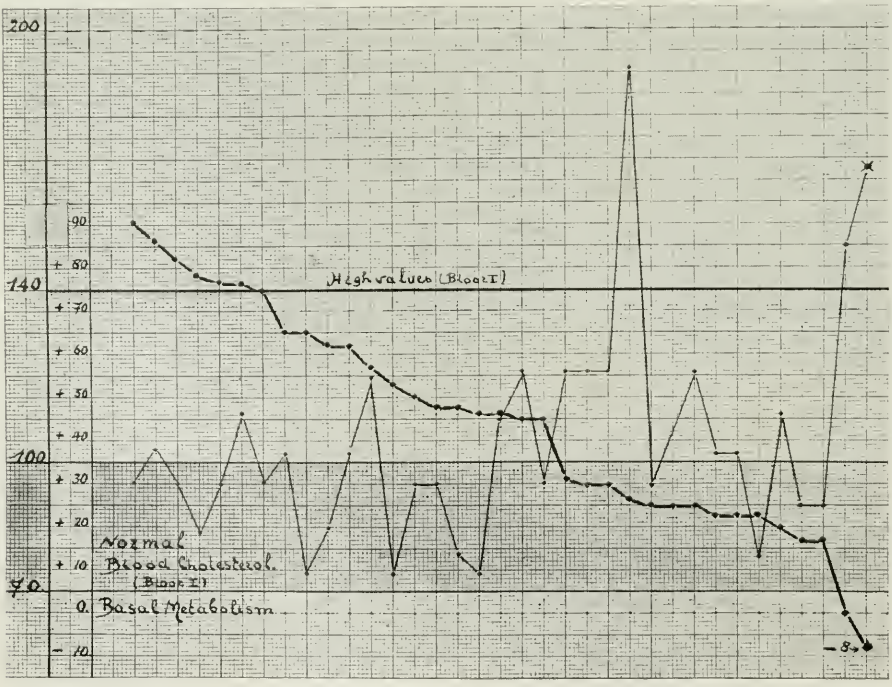

Fig. 9.—*Relation of the rate of basal metabolism and blood cholesterol (Bloor I values) in exophthalmic goiter.* (35 cases.) Observe that high basal metabolism and relatively low (normal) blood cholesterol values coincide as a whole. Only three cases exceed the "high" cholesterol line (140 mg.); the first case (from the left) was a highly excitable patient, and could not be induced to remain quiet during the calorimetric test, her metabolic rate contains an element due muscular activity; in the two other cases the high cholesterol values are accompanied by a normal and slightly subnormal metabolic rate.

terol is oxidized and disintegrated by the action of light. It is known that radium is photoactive. It is possible, therefore, that the photochemical activity of radium may cause the changes observed in the cholesterol content of the blood after radium treatment. The increase of the cholesterol split products in the blood, namely, the increased difference between Bloor I and II, supports this interpretation.

If we compare the disintegration of cholesterol in the body to the combustion of fuel by fire, changed or oxidized cholesterol may be compared to fuel that has been consumed and thus rendered harmless, whereas pure, unchanged cholesterol may be compared to fuel that has not yet been consumed.

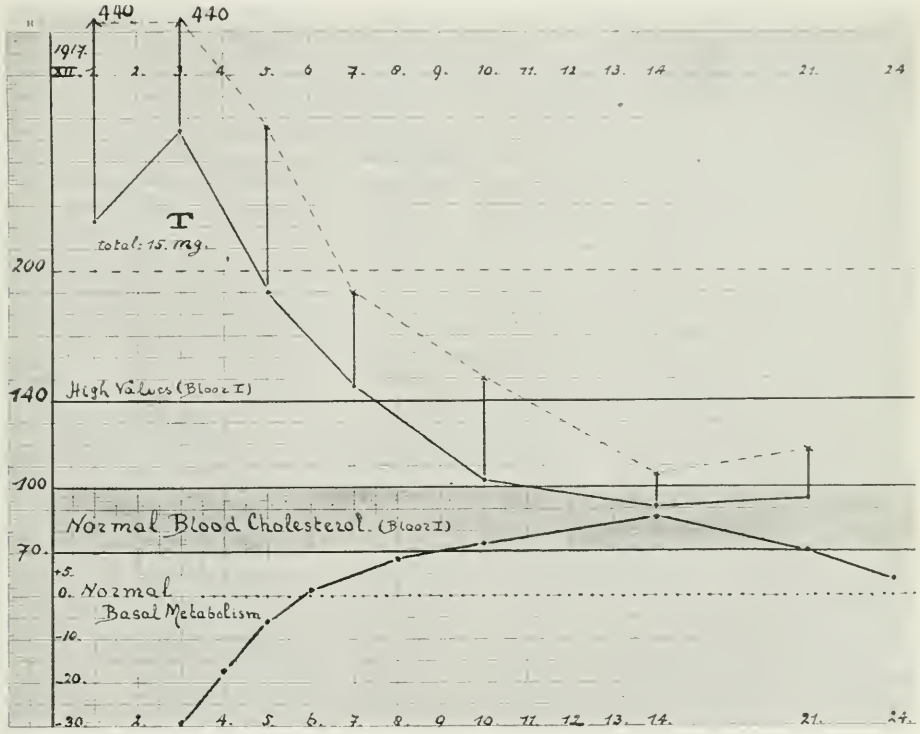

Fig. 10.—*Effect of the administration of the thyroid hormone (Kendall's Thyroxin) in myxedema* (1 case).

— . — . Bloor I test.

– – – . – – – . Bloor II test.

T - Thyroxin 15 mg. at one dose.

Observe the decrease of the Bloor I values which runs parallel to the increase of the rate of basal metabolism, and is similar to the effect of radium on the Bloor I values. That the increase of the Bloor II values is less marked than after radium treatment is probably due to the very rapid rate of elimination during the temporary condition of hyperthyroidism caused by the administration of the thyroid hormone in myxedema. Patient greatly improved.

An accumulation of unconsumed fuel contains in itself the latent possibility of starting a conflagration. It is possible that, although we know pure cholesterol promotes cell division, changed cholesterol may fail to do so. A high percentage of unchanged cholesterol, such as is found in carcinoma, would therefore represent an opportunity for undue cell proliferation that is an element of danger. This danger appears to be reduced or eliminated by the action of

radium since it is found that the amount of changed (possibly harmless) cholesterol increases in the blood as the condition of the patient is improved by radium therapy.*

The reduction of the blood cholesterol values by the administration of the thyroxin in myxedema, however, can not be looked upon as the result of photochemical activity. The thyroid hormone is not photoactive. Nevertheless the blood cholesterol values are lowered by the use of thyroxin as well as by radium treatment. We know that the thyroid hormone is capable of increasing the rate of basal metabolism, and Figs. 10 and 11 show that increased metabolism is accompanied by a reduction of the cholesterol content (Bloor I) of the blood, similar to that produced by radium

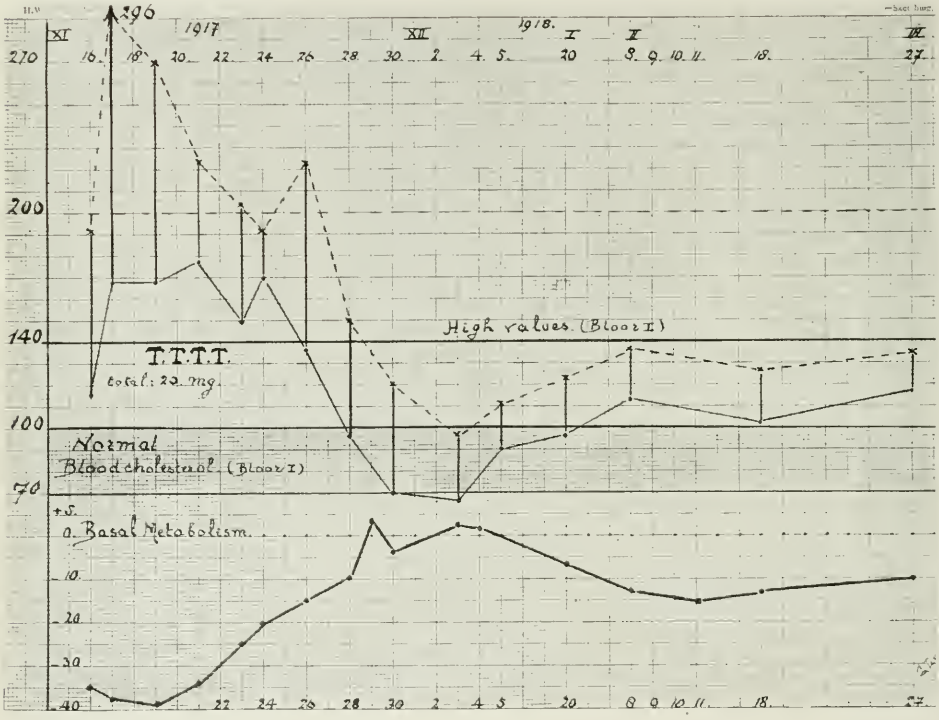

Fig. 11.—(The same as Fig. 9.) T - thyroxin 5 mg. at each dose. Patient went home perfectly well.

treatment. This fact, whatever the chemical or physiologic process to which it is due may prove to be, shows that the effect of thyroxin on the chemical composition of the blood is similar to that of radium. It also suggests that, since the beneficial effects of radium therapy are well known, the condition of patients suffering from carcinoma may be improved by the administration of thyroid hormone. The relation of thyroid activity to the development of car-

*Shortly after this paper was read, T. Brailsford Robertson published his observations on cholesterol derivatives, which appear to confirm the above interpretation. (*Journal of Cancer Research*, 1918, iii, 74-90.) Robertson found that by substituting the OH group of the hydroxybenzol radical in the cholesterol molecule he obtained substances which did not accelerate the growth of tumor grafts, whereas he had demonstrated previously that the unchanged cholesterol molecule was capable of so doing. His conclusion should be read in the original article as it is impossible to do justice to the importance of his observations in this brief reference to them.

cinoma has often been discussed,[72] but so far as I am aware, the influence of thyroid activity on the cholesterol content of the blood has not been taken into consideration in relation to cancer. The following facts are noteworthy, however: Fourteen cases of spontaneous recovery from cancer in man have been reported by Gaylord and Clowes[16] and two similar cases have occurred to my knowledge* (a microscopic diagnosis was made in every instance). The patients in question had been pronounced "hopeless cases" and received no further treatment. Nevertheless their condition improved to such an extent that they could be looked upon as "cured" from a clinical as well as from a practical point of view. The deduction seems admissible that these patients were able in some way to recover their metabolic balance, notwithstanding the fact that there appeared to be no hope for them. We know that in the majority of instances carcinoma occurs when the first vigor of youth is past, and when metabolism in general tends to become sluggish; when the body, in fact, might be compared to a badly burning fire. The decrease of metabolic activity, caused or accompanied by a decreased functional activity of certain glands, is likely to result in the retarded combustion of the substances that are taken in with the food. It has been shown that the cholesterol content of the blood can be increased and reduced at will by the composition of the diet.[41] The administration of a hormone which is known to increase the metabolic rate might therefore provide the stimulus which the body itself is incapable of supplying and by increasing metabolism assist the body in recovering its balance of health. If in sixteen cases the human body has proved itself equal to this task without assistance it might be able to do so in others with the right kind of assistance. The deduction seems logical; time alone can show if it is correct..

SUMMARY

Cholesterol promotes cell multiplication; high blood cholesterol values must, therefore, further malignant growth. High blood cholesterol values are commonly found in carcinoma. Radium treatment and the administration of the thyroid hormone both reduce the cholesterol content (Bloor I) of the blood, and increase the amount of changed cholesterol in the blood (namely, the difference between the Bloor I and II values). The high cholesterol values in myxedema are brought down to normal by the administration of the thyroid hormone at a rate parallel to the rise in basal metabolism induced by the latter.

CONCLUSIONS

1. The test for cholesterol in the blood is not a diagnostic but merely a clinical test giving valuable information concerning cholesterol metabolism.

2. The high cholesterol values commonly found in carcinoma are not due

*One was an inoperable case of pelvic carcinoma, in which the cancer was found to have disappeared several years later at an emergency laparotomy by Kümmel (personal communication by H. R. Gaylord); the other a case of sarcoma of the stomach, the patient operated on at the Brooklyn Hospital, New York, in 1908. The patient was not expected to live beyond two years but is well and active today. His history will be reported when the details of the case have been obtained. In both cases a microscopic diagnosis was made. H. R. Gaylord expressed the opinion that spontaneous recovery from carcinoma would not be found as uncommon as is generally believed, if surgeons were able to keep track of all their patients.

to cell destruction, since they are reduced by radium treatment, although radium causes cell destruction; they must therefore be due to a disturbance of cholesterol metabolism.

3. The disturbance of cholesterol metabolism may be but an evidence of a subnormal rate of basal metabolism, since the high cholesterol values in myxedema are reduced by the administration of the thyroid hormone (thyroxin) by which the rate of basal metabolism is greatly increased.

4. The disturbance of cholesterol metabolism in carcinoma is revealed by the absence of changed cholesterol or cholesterol split products in the blood of a high percentage of cancer patients, as is shown by the lack of a difference between the cholesterol values obtained by the Bloor I and Bloor II methods, since the writer constantly found such a difference in normal blood and in pathologic but nonmalignant conditions.

5. Radium treatment by reducing the unchanged cholesterol (Bloor I values) and increasing the changed cholesterol (difference between Bloor I and II values) affects the chemical composition of the blood; a fact that has not hitherto been taken into account, but which may play an important part in the beneficial effect of radium therapy.

6. Thyroxin affects the blood cholesterol values in a manner similar to that of radium and may therefore also be expected to improve the condition of patients suffering from carcinoma. Careful investigation will, however, be needed before definite conclusions can be drawn concerning the effect of thyroxin on carcinoma as various metabolic factors may have to be taken into account.

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LABORATORY METHODS

NOTE ON METHODS FOR PREPARING ISOAMYL ISOVALERATE; A SATISFACTORY SUBSTANCE TO PREVENT FOAMING

By C. H. Fiske

THE unavailability of caprylic alcohol at the present time makes it desirable that simply prepared substitutes should be described. Isoamyl isovalerate is equally as efficacious as caprylic alcohol, and can be prepared by the following methods.—*J. J. R. Macleod.*

FIRST METHOD

To 35 c.c. commercial isovaleric acid add 4 gm. anhydrous calcium chloride. Shake the mixture until it has separated into two layers, and most of the calcium chloride has dissolved. The greater part of the water is in this way removed. Decant off the upper layer, and transfer 28 c.c. of this to an Erlenmeyer flask, of about 200 c.c. capacity, containing a few glass beads. Add 30 c.c. isoamyl alcohol, and 1 c.c. concentrated sulphuric acid. Connect the flask with a reflux condenser, and boil for one hour over a wire-gauze. Cool, transfer to a separatory funnel, and draw off the lower layer. To the upper layer add water, and shake the mixture thoroughly with solid sodium carbonate, until a sample of the aqueous layer, drawn off through the stem, is found to be alkaline to phenolphthalein. Separate again, and remove the excess sodium carbonate by washing with water. After drawing off the final wash-water (which should not be alkaline to phenolphthalein), filter the residual liquid. The filtrate is then ready for use. It will, however, keep better if dried with calcium chloride and distilled.

SECOND METHOD

Dissolve 50 gm. potassium dichromate in 200 c.c. boiling water. Cool under the tap, with constant shaking. The greater part of the dichromate will separate out in small crystals. Add 50 c.c. isoamyl alcohol. While the mixture is kept constantly agitated under the tap, now add 70 c.c. concentrated sulphuric acid, at such a rate that the temperature does not rise above 30°. Let stand at room temperature overnight. Separate the two layers, transferring the upper one to a 500 c.c. distilling flask. Add 200 c.c. water, and distill through a water-cooled condenser, until all of the ester has come over. Neutralize the distillate with sodium carbonate, wash with water, etc., as in the first method.

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EDITORIALS

With the American Red Cross at the Front

ARM and leg wounds compose a large majority of the injuries received in battle, hence there is an enormous demand for splints—a framework upon which the injured member may rest in the most comfortable position.

Contrary to the layman's preconceived opinion of a splint, it is not a piece of wood, but, for the use of the American Army, is of steel framework with leather and felt padding. And most of them are of ingenious invention, being far from simple affairs. The types are almost as numerous as the injuries for which they are made to aid in healing.

The American Red Cross has taken over the job of supplying all splints to the American Expeditionary Forces, and in the vernacular of the streets, it is "some job." The demand for these particular articles is increasing at a great rate due to the increasing activity of American troops on the battle front.

To meet this demand the Red Cross has established a splint manufacturing plant of its own in a large French town not far from the battle front.

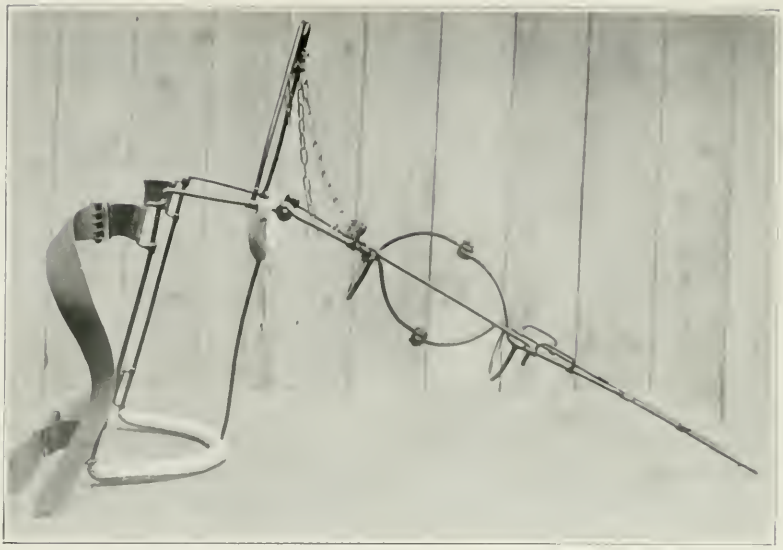

Fig. 1.

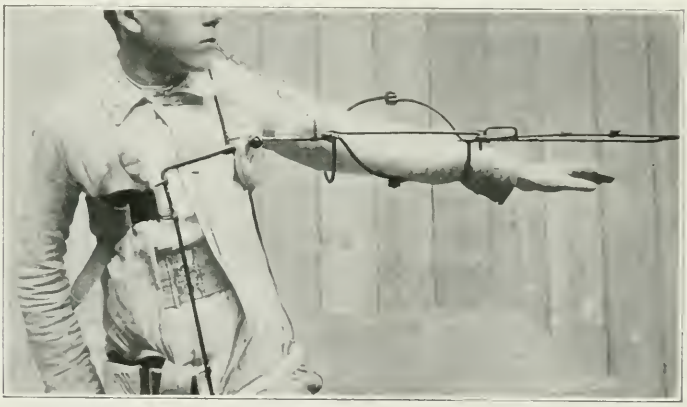

Fig. 2.

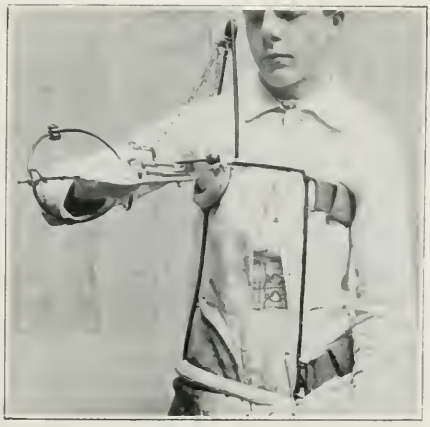

Fig. 3.

The new adjustable abduction arm splint for use in base hospitals in arm fractures for the perfection of which the American Red Cross splint department has been largely responsible. The advantages of this splint are that it can be used for either arm and can be adjusted to any position.

While the splint construction is not complicated, it must be exceedingly careful and delicate. The splints that fit on the upper portion of the leg or arm must be carefully padded with felt and sheepskin. This work is done by French women and by hand.

Most of the leg and arm splints are made of steel rods bent in the shape of a U and are about four feet in length. They taper from the bottom up to the top where a semi-circular steel rod, attached to each end of the U by a hinge, is padded well and attached. Upon the padded part rest the thigh or shoulder of the injured member. The wounded or broken leg or arm is bandaged between the two sides of the U. The bottom of the U is dented in order that a bandage may be attached to the bottom of the splint and the injured member for the purpose of pulling or applying the necessary weight to force the broken bones or torn muscles into place. It also serves to attach the splint to the foot of a bed or the front of an ambulance so that the wounded leg or arm may be elevated to any position which will give the greatest comfort to the sufferer.

There are numerous variations of this basic splint. Some have a hinge in the center of both sides of the U, so that an injured leg or arm may be bent at the knee or elbow and bound into position. Some have a hand rest at the end, by which the hand may be bandaged into an immovable position, so that injured muscles will not be moved by unconscious effort. Then there is the U splint with an unmovable padded steel circle at the top, which fits close to the leg or shoulder crotch. A splint of this type is also made with hinges so that the arm or leg, stretched straight and fast, may be moved at the thigh or shoulder. There are small wire splints for the foot, the hand and the wrist.

All of them are made by hand in this factory, because of the lack of machinery. Even the welding and varnishing of the steel and wire, as well as the nickeling, is done in the Red Cross factory.

This is only one of the many activities from which the American Red Cross has relieved the Army. During the past few months the Red Cross has been forced to let contracts to various private manufacturers to furnish a sufficient supply of these necessary hospital appliances. But with the growth of its organization, it has established its own manufactory in the war zone of France, in order that there may be fewer transportation delays and better service in the work of relieving as much suffering as possible among American wounded.

The Journal of Laboratory and Clinical Medicine

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ORIGINAL ARTICLES

THE CLINICAL PATHOLOGY OF MUSTARD GAS (DICHLORETHYL-SULPHIDE) POISONING*

BY GEORGE R. HERRMANN, M.S., M.D., ANN ARBOR, MICHIGAN

IN the rapidly accumulating mass of literature on war gassing there are practically no reports on the clinical laboratory aspects of the condition. Even the most ordinary routine examinations as practiced daily in the smallest civilian hospital are unrecorded in the clinical reports on gassing sent from the front. Occasionally in the French reports some fragmentary laboratory observation is included. Mandel and Gibson[1], speaking of the complications of mustard gas poisoning say that albuminuria is not uncommon, but that true nephritis has been rare in their experience. They comment that this is remarkable considering the frequent extensive burns of skin and mucous membranes. Pissarello[2] reports that in his series of sixty cases the urine was always negative to tests for sugar and albumin. If the observations on the urinary changes are few, as shown by the preceding, those on the blood changes are still more rare. Miller[3] has recorded observations on the blood changes found in the more or less chronic stages of gassed cases; and, although not specifically stated, some of these may have been cases of mustard gas poisoning. The exigencies of field and camp, of the field and base hospital, in the active sectors where cases of gassing would be met, have undoubtedly been such as to necessitate a sacrifice of the laboratory aspects of the condition. Further, the lack of complete laboratory facilities for the routine and special examinations, as well as of trained laboratory workers, would discourage attempts in this line of research.

Through the cooperation of Captain Lester Roos, and at the request of Doctor A. S. Warthin an opportunity was afforded me of making observations upon

*From the Pathological Laboratory of the University of Michigan, Ann Arbor, Michigan.

the blood and urinary changes in a series of cases gassed with mustard gas. In thirty cases, we were fortunate in having a very interesting variety from the most severe types, those which resulted fatally, to those showing only the slightest lesions such as the most mild type of conjunctivitis. Nine of the severe cases, on whom the observations were fairly complete, and a tenth group of the mild cases, will be reported at this time. The latter suffered only from conjunctivitis and minor burns of the hands and fingers, and time did not permit any extensive study of this type of case. Unfortunately, our cases were not accessible until the tenth day after the gassing, and then no clinical laboratory was at hand in which our work could be carried out. Further, the more or less inaccessibility of the camp made the organization and maintenance of the laboratory a problem. The lack of adequate assistance during the emergency also rendered it impossible for us to do the laboratory work as completely as we had hoped. Nevertheless, we succeeded in getting a fairly complete record of the disturbances of function in the severe cases. The results determined the management and application of therapeutic measures, and the favorable effects of the instituted treatment were likewise noted. Another encouraging feature of this work is the definite and constant regularity of the results. The step-like gradation in the severity of the cases finds a parallel in the results of the various laboratory examinations; and the changes in the blood and urine show a gradual improvement, uniformly, under the adopted methods of treatment.

THE LABORATORY TESTS AND METHODS EMPLOYED

The laboratory work was carried out according to the routine methods of any well-regulated hospital. Daily complete 24-hour urine specimens were collected in clean, well corked, dark glass, two liter bottles, each patient having his own bottle throughout the period in the hospital. The urine samples were examined daily. The specimen was measured and mixed in a graduated glass cylinder. The physical characteristics of the urine were noted and the reaction to red and blue litmus paper was determined. The specific gravity was taken with a urinometer graduated for work at room temperature. A sample of urine was tested for reducing substances, especially glucose, with Fehling's solution. The specimens were very carefully examined for albumin, routinely, by the Heller's fuming nitric acid ring test, and the acetic acid (8 per cent) and potassium ferrocyanide method. In many instances, and especially, if there was any question as to the reaction, the heat and nitric acid, and the heat and acetic acid (3 per cent) tests, were used. The dilute ferric chloride test for the heat labile, Burgundy-red reaction of diacetic acid, as the index of acidosis, was carried out for some time in each case.

An estimate of the renal function or efficiency was obtained by the quantitative percentage determination of urea and sodium chloride, and the calculation of the daily 24-hour output of these substances, in the daily 24-hour urinary excretion.

The quantitative urine urea was determined in each case by the method of Marshall and Van Slyke in which urease, the urea splitting enzyme, obtained from the soy bean, is used to hydrolyze the urea and yield ammonia.[4, 5, 6, 7] The quantitative urine chloride estimations were made by the modified Volhard's method, in which the albumin-free urine is titrated against a solution of silver nitrate, containing 29.06 grams per liter, 1 c.c. of this solution, corresponding to 0.01 grams of sodium chloride. The ammonium thiocyanate solution used to estimate the excess of the $AgNO_3$ solution used by titration was of such a strength that 2 c.c. neutralized 1 c.c. of the silver nitrate solution. The nitric acid and iron salt indicator was used.[4, 5, 6, 7]

A few of the special examinations and tests were made on the urines. The diazo reaction of Ehrlich with sulphanilic hydrochloric acid and sodium nitrite was tried regularly for a part of the course of each case. Likewise a test for urobilinogen with paradimethylamino-benzaldehyde was carried out fairly routinely, as long as the reagent was at hand. The bromine water oxidizing method was used in the examination of the urine for melanin. Gmelin's nitric acid test and the foam test for bile pigments were employed

in each case. Besides this complete chemical examination the centrifugated sediment of the urine was regularly and carefully examined microscopically.

The functional efficiency of the kidneys was further determined by estimating the percentage of phenolsulphonephthalein that was excreted, when the Rowntree and Geraghty renal functional test was applied. The quantitative estimations were made with a Dunning colorimeter. Unfortunately, the phenolsulphonephthalein and the colorimeter apparatus could not be obtained until late, that is, when the patients were convalescing.

Another index of the secretory ability of the kidney was determined by the estimation of the quantity of urea in the blood. Van Slyke's modification of Marshall's urease method was employed in this procedure as it had been in the case of the urine urea determinations. The usual enumeration of red and white blood cells, differential counting of the leucocytes and estimation of the hemoglobin were carried out. The red and white blood cells were counted in a Thoma-Zeiss hemacytometer. The hemoglobin was estimated by a Gower-Sahli hemoglobinometer and a Tallquist scale. Cover-glass blood smears were made and the preparations were stained with Wright's blood stain for differential counting. The sputum and stools were examined when indicated.

Culture media were not at hand for a complete bacteriologic examination in these cases. In the marked stage of secondary furunculosis, many smears from very young furuncles and also smears of the pus in the more mature lesions were made and stained with various staining solutions.

THE CASES

The material has been arranged and is presented according to the severity of the cases. Beginning with Case I, the most severe, each succeeding case, in order, is less severe down through the nine cases. The seven severe cases were all gassed on the same day, June 27, but were seen for the first time by an army medical man on July 4. In Case Group No. X all four members of which are very mild, this same order is maintained; Case X-A being the most severe of that group, and the last case practically an untouched individual, who had been with the other men, but who was apparently unsusceptible to the concentrations to which the other men had reacted. The remainder of the thirty cases were similarly very mild and the laboratory examinations revealed no departures from the normal.

The blood pressure readings were not made, because the severe skin burns and especially the deep ulcerations in the bends of the elbows, made the procedure too painful in the more serious cases and it was not considered worth while in the mild ones.

The temperature, pulse and respiration tables for each case are followed by the laboratory data of the changes in the urine, blood urea and blood, with other special examinations according to the indications.

Case I.—Patient had been severely gassed ten days before and was moribund when the blood specimen was taken. Death occurred nine hours later. Almost the entire skin surface was involved; secondary infection was marked, and a foul-smelling gangrenous layer, saturated with pus, covered the body.

Temperature, Pulse, and Respiration

		T.	P.	R.
June 27	7:30 P.M.	97.6	90 (?)	20 (?)
June 28		98.5	99 (?)	20 (?)
June 29		98.8	99 (?)	20 (?)
June 30		99.8	104 (?)	20 (?)
July 1	A.M.	100.	105 (?)	20 (?)
July 2	A.M.	98.2	87 (?)	20 (?)
	P.M.	102.	152	28
July 3	6:00 A.M.		124	
	12:00 M.	100.6	110	28 (?)
	6:00 P.M.	102.8	128	28 (?)

TEMPERATURE, PULSE, AND RESPIRATION (*Cont'd*)

			T.	P.	R.
July	4	A.M.	101.6	158	28 (?)
		P.M.	103.2	150	28 (?)
July	5	A.M	104	140	26
		4:00 P.M.	103.6	152	26
		9:00 P.M.	104	162	28
July	6	8:00 A.M.	103	140	28
		12:00 M.	103	142	28
		4:00 P.M.	102.4	136	24
		7:45 P.M.	100	136	28
		10:15 P.M.	101	136	32
July	7	2:00 A.M.	100.2	140	28

URINE AND BLOOD UREA

	PHYSICAL AND CHEMICAL CHARACTERISTICS OF THE URINE			SUGAR GLUCOSE	ALBUMIN	ACIDOSIS DIACETIC ACID		RENAL FUNCTIONAL EFFICIENCY				DIAZO SUB.		PIGMENTS		
DATE	URINE OUTPUT AMT. IN 24 HRS.	REACTION	SPECIFIC GRAVITY	FEHLING'S SOL.	HELLER'S HNO_3 RING TEST	ACETIC AC. FERROCYANIDE	FERRIC CHLORIDE	QUANT. UREA GM. PER 100 C.C.	QUANT. CHLORIDE GM. PER 100 C.C.	UREA OUTPUT IN 24 HRS.	CHLORIDE OUTPUT IN 24 HRS.	SULPHANILIC AC. EHRLICH'S DIAZO	DIMETHYLAMINOBENZALDEHYDE UROBILINOGEN	BROMIN WATER MELANIN	GMELIN'S TEST FOR BILE	FOAM TEST FOR BILE
July 7	60 c.c.	P.M.* Acid (Anuria**)	1020	Neg.	Pos.	Pos.	Neg.	0.13	0.18	—	—	—	—	—	—	—
7	BLOOD UREA P.M. .1104 gm. Urea per 100 c.c.															
7	COLOR OF URINE Dirty yellow. Turbid.				URINARY SEDIMENT Great showers of granular casts. Many fragmented casts. Much debris. Masses of epithelial cells (bladder and few renal). Leucocytes. Clusters of red blood cells. Amorphous urates.											

*P.M. Bladder urine postmortem.
**Patient practically had had anuria during the last twenty-four hours of life.

BLOOD

Erythrocyte count,		3,650,000
Hemoglobin,		70%
White cell count,		13,200
Differential White Count:		
Polynuclears		
Neutrophile	88%	
Eosinophile	4%	
Lymphocytes		
Large	1%	
Small	2%	
Transitionals	2%	
Myelocytes, Neutrophile	3%	

The blood platelets were not increased. The red cells show no changes. No nucleated red cells were found.

CASE II.—This was likewise a case of very severe gassing. The first blood count was made eleven days after being gassed. At that time there was a diffuse suppurative gangrenous process resulting from an extreme secondary infection of the necrosing skin. Active measures were taken to lessen the degree of the pyogenic process. The last blood count was done on the day of his death, four weeks after gassing.

TEMPERATURE, PULSE, AND RESPIRATION

		T.	P.	R.
June 30		98.	72	20
July 1		100.4	105	24
July 2	A.M.	98.6	80	20
	P.M.	98.8	100	18
July 3	A.M.	100.6	112	24
	P.M.	100.8	110	20
July 4	A.M.	102.6	100	20 (?)
July 5	5:00 A.M.	102.6	158	32
	4:00 P.M.	103.6	160	32 (?)
	9:00 P.M.	103.	152	34
July 6	4:00 A.M	103.	148	32
	12:00 M.	103.	150	32 (?)
	4:00 P.M.	101.	152	28
	5:45 P.M.	103.6	152	28
July 7	4:30 A.M.	102.2	148	36
	7:00 A.M.	102.	148	38
	1:00 P.M.	102.2	140	36 (?)
	4:30 P.M.	101.6	150	36
	8:30 P.M.	102.4	152	38
	10:30 P.M.	100.	150	34
July 8	4:00 A.M.	102.6	152	36
	8:00 A.M.	103.	136	36
	1:00 P.M.	102.2	138	38
	4:00 P.M.	100.	136	36
	8:00 P.M.	103.4	140	38
July 9	4:00 A.M.	101.6	148	38
	7:30 A.M.	100.8	148	38
	12:00 M.	100.2	116	28
	4:00 P.M.	100.8	104	30
	8:00 P.M.	100.4	120	32
	12:00 P.M.	100.5	122	32 (?)
July 10	4:00 A.M.	100.6	118	30
	8:00 A.M.	100.6	128	32
	12:00 M.	100.4	120	30
	4:00 P.M.	101.	130	30
	7:45 P.M.	102.4	128	27
	12:00 P.M.	101.2	122	28
July 11	4:00 A.M.	100.8	126	25
	12:00 M.	101.	136	36
	4:00 P.M.	103.	130	32
	7:00 P.M.	101.		
	8:30 P.M	99.	120	26
July 12	12:30 A.M.	99.4	133	28
	4:00 A.M.	99.2	120	26
	8:00 A.M.	100.8	106	30
	10:00 A.M.	101.2		
	12:00 M.	108.8	126	26
	3:00 P.M.	100.4		
	4:00 P.M.	102.3	130	34
	5:30 P.M.	100.4		
July 13	1:30 A.M.	101.	120	
	5:00 A.M.	102.4	124	
	7:00 A.M.	100.	118	22
	8:00 A.M.	101.2	120	24
	12:00 M.	102.2	126	30
	2:30 P.M.	102.2	128	30
	4:00 P.M.			
	5:00 P.M.	103.	132	30
	8:00 P.M.	102.	130	30
	10:00 P.M.	102.	134	30
	11:15 P.M.	102.	130	
July 14	2:00 A.M.	100.6	124	28
	3:00 A.M.			
	4:00 A.M.	100.2	126	24
	6:00 A.M.			

TEMPERATURE, PULSE, AND RESPIRATION (*Cont'd*)

		T.	P.	R.
July 14	8:00 A.M.			
	12:00 M.	101.	124	
	4:00 P.M.	102.5	140	34
	8:00 P.M.	102.	130	
	10:00 P.M.	103.	132	
	10:45 P.M.	103.5	130	
July 15	3:30 A.M.	101.	126	24
	6:00 A.M.			
	7:00 A.M.	100.5	118	24
	12:00 M.	103.6	134	30
	4:00 P.M.	102.5	140	34
	8:30 P.M.	102.2	125	
	9:00 P.M.	103.2	126	
	12:00 P.M.	102.2	97	
July 16	1:00 A.M.	101.2	100	
	4:00 A.M.	101.6	115	
	5:00 A.M.	101.8	119	
	7:00 A.M.	100.	121	
	8:00 A.M.	106.6	128	34
	12:00 M.	101.	116	32
	4:00 P.M.	102.2	110	
	8:00 P.M.	103.	120	
	10:00 P.M.	99.8	124	
	10.30 P.M.	99.8	125	
	11:00 P.M.		110	
	11:30 P.M.		120	
	12:00 P.M.	102.	115	
July 17	12:30 A.M.			
	2:30 A.M.	102.6	116	
	4:00 A.M.	101.2	115	
	4:30 A.M.			
	5:00 A.M.	101.2	126	
	6:00 A.M.	99.2	126	
	8:00 A.M.	100.6	120	30
	12:00 M.	100.4	112	28
	4:00 P.M.	100.4	128	28
	8:00 P.M.	101.8	125	
	10:00 P.M.	99.8	120	
	12:00 P.M.	101.	120	
July 18	2:00 A.M.	98.8	115	
	4:00 A.M.	98.8	120	
	8:00 A.M.	100.	126	32
	1:00 P.M.	100.4	116	28
	5:00 P.M.	100.6	128	
	8:00 P.M.	101.8	120	
	12:00 P.M.	102.	130	
July 19	4:00 A.M.	100.2	124	28
	8:00 A.M.	100.	128	28
	1:00 P.M.	100.6	120	28
	4:00 P.M.	101.4	120	28
	8:00 P.M.	101.6	120	
	12:00 P.M.	101.6	120	28
July 20	4:00 A.M.	101.4	125	
	4:30 A.M.	100.2		
	8:00 A.M.	99.8	120	30
	12:00 M.	100.2	124	32
	4:00 P.M.	101.4	124	34
	8:00 P.M.	102.2	120	
	10:00 P.M.	101.2	124	
	12:00 P.M.	101.2	125	
July 21	4:00 A.M.	101.4	120	
	6:00 A.M.	99.8	105	

TEMPERATURE, PULSE, AND RESPIRATION (*Cont'd*)

		T.	P.	R.
July 21	8:00 A.M.	99.8	124	30
	12:00 M.	101.2	124	30
	4:00 P.M.	101.6	128	32
	8:00 P.M.	102.4	130	
	10:00 P.M.	100.	120	
	12:00 P.M.	101.6	122	
July 22	2:00 A.M.	100.2	124	
	4:00 A.M.	101.2	126	
	6:00 A.M.	98.6	120	
	8:00 A.M.	99.6	130	36
	11:00 A.M.		136	50
	12:00 M.	101.6	140	50
	4:00 P.M.	102.	152	52
	5:00 P.M.		160	58

URINE AND BLOOD UREA

	PHYSICAL AND CHEMICAL CHARACTERISTICS OF THE URINE			SUGAR GLUCOSE	ALBUMIN		ACIDOSIS DIACETIC ACID	RENAL FUNCTIONAL EFFICIENCY				DIAZO SUB.		PIGMENTS		
DATE	URINE OUTPUT AMT. IN 24 HRS.	REACTION	SPECIFIC GRAVITY	FEHLING'S SOL.	HELLER'S HNO_3 RING TEST	ACETIC AC. FERROCYANIDE	FERRIC CHLORIDE	QUANT. UREA GM. PER 100 C.C.	QUANT. CHLORIDE GM. PER 100 C.C.	UREA OUTPUT IN 24 HRS.	CHLORIDE OUTPUT IN 24 HRS.	SULPHANILIC AC. EHRLICH'S DIAZO	DIMETHYLAMINOBENZALDEHYDE UROBILINOGEN	BROMIN WATER MELANIN	GMELIN'S TEST FOR BILE	FOAM TEST FOR BILE
July	c.c.										G.					
8	1850	Acid	1018	Neg.	Pos.?	Pos.?	Neg.	—	0.16	—	2.96	—	—	—	Neg.	Neg.
9	1470	"	1024	Neg.	Pos.	Pos.	Neg.	—	0.24	—	3.53	—	—	—	Neg.	Neg
10	1000	"	1020	Neg.	Pos.	Pos.	Neg.	0.53	0.10	5.30	1.00	—	—	—	Neg.	Neg.
11	1650	"	1012	Neg.	Pos.	Pos.	Neg.	—	0.22	—	3.33	Neg.	—	Neg.	Neg.	Neg.
12	1150	"	1013	Neg.	Pos.	Pos.	Neg.	0.74	0.40	8.51	4.60	Neg.	—	Neg.	Neg.	Neg.
13	1200	"	1015	Neg.	Pos.?	Pos.	Neg.	0.38	—	4.56	—	Neg.	—	Neg.	Neg.	Neg.
14	2000	"	1011	Neg.	Pos.	Pos.	Neg.	1.80	—	36.0	—	Neg.	—	Neg.	Neg.	Neg.
15	— *	"	1015	Neg.	Pos.	Pos.	Neg.	1.35	—	—	—	Neg.	—	Neg.	Neg.	Neg.
16	1550	"	1013	Neg.	Pos.	Pos.	Neg.	0.54	0.30	8.37	4.65	Neg.	Pos.	Neg.	Neg.	Neg.
17	500*	"	1024	Neg.	Trace	Trace	Neg.	—	0.50	—	2.50	—	Pos.	—	Neg.	Neg.
18	730*	"	1020	Neg.	"	"	Neg.	0.84	0.52	6.16	3.79	—	Pos.	—	Neg.	Neg.
19	750*	"	1015	Neg.	"	"	Neg.	0.54	0.66	4.05	4.95	—	Neg.	—	Neg.	Neg.
20	800*	"	1013	Neg.	Neg.	Neg.	Neg.	—	0.44	—	3.52	—	—	—	—	—
21	1075*	"	1007	Neg.	Trace	Trace	Neg.	0.35	0.54	3.76	5.80	—	—	—	—	—
22	1475*	"	1008	Neg.	"	"	Neg.	—	0.42	—	6.19	—	—	—	—	—

BLOOD UREA

10 .036 Gm. per 100 c.c.

	COLOR OF URINE	URINARY SEDIMENT
8	Deep red brown.	Amorphous urates. Few granular casts. Bladder and kidney epithelial cells. Many leucocytes. Few red blood cells.
11	Brownish yellow.	Amorphous urates. Granular casts. Leucocytes. Epithelial cells, plus the sediment of some alkaline fermentation—triple phosphates especially.
13	Dark brown.	Excess of uric acid crystals. Amorphous urates. Large number of red blood cells. Few granular casts and epithelial cells.
15	"	Incontinence, no specimen collected.
16	Amber	Much improved. Amorphous urates. Leucocytes. Few fragmented granular casts. Epithelial cells. Few bacteria (contamination). No red blood cells.
17	Dark amber.	Few amorphous urates. Few leucocytes. Few granular and epithelial cells. Bacteria.
18	"	Excessive amount of uric acid and amorphous urates coloring the sediment bright red. Few leucocytes. Few granular casts. Few renal epithelial cells.
19	Light amber.	Sediment is much improved. Few amorphous urates. Few granular epithelial cells. Few leucocytes. One or two hyaline casts.
20	Amber.	Apparently much improved. Few amorphous urates. Leucocytes, and granular epithelial cells.
21	"	Abundant urates. Few hyaline and fragmented granular casts. Few granular epithelial cells. Few leucocytes.
22	"	Large amount of amorphous urates. Many uric acid crystals. Numerous hyaline casts and renal epithelial cells. Few red and white blood cells.

*Incontinence.

	Erythrocyte count	Blood White count	Hemoglobin
July 8	4,100,000	29,700	75%
July 11	4,250,000	21,500	80%
July 14	.....	13,000	....
July 15	.....	13,500	....
July 18	.....	13,000	....
July 20	.....	12,700	65%
July 22	.....	10,800	....

Differential white count on July 11, 14 days after gassing.

Polynuclears	
Neutrophile	86.5 %
Eosinophile	6.75%
Basophile	.5 %
Degenerates	.75%
Lymphocytes	
Large	.25%
Small	.75%
Transitionals	.5 %
Large basophilic mononuclears	1.0 %
Myelocytes	
Neutrophile	2.5 %
Eosinophile	.25%
Myeloblasts	.25%

The polymorphonuclears are chiefly young types, showing the Arneth scale to the left. The eosinophilia is marked. The blood platelets are large and numerous. One megaloblast was found in counting four hundred white cells. No other changes in the red cells were noted.

Case III.—This patient was very severely gassed. He early developed a severe secondary infection with diffuse suppuration. There was also an extensive bronchopneumonia. After institution of active treatment by irrigation and continuous baths, the pyogenic process rapidly cleared up. Recovery after two months. The first blood count was made two weeks after gassing, and the last, four weeks after gassing.

Temperature, Pulse, and Respiration

		T.	P.	R.
June 28	A.M.	99.4	90	28
	P.M.	99.8	100	30
June 29	A.M.	100.	110	28
	P.M.	100.	110	28
June 30	A.M.	99.8	109	28 (?)
	P.M.	97.	104	28
July 1	A.M.			
	P.M.	100.8	108	26
July 2	A.M.	99.2	105	28
	P.M.	100.8	108	26
July 3	A.M.	101.	108	26
July 4	A.M.	99.6	109	18
July 5	4:00 A.M.	103.4	128	28
	4:00 P.M.	102.6	128	24
	9:00 P.M.	103.	132	30
July 6	4:00 A.M.	102.	132	26
	12:00 M.	102.	128	32
	4:00 P.M.	103.	132	28
	10:00 P.M.	102.4	120	24
July 7	2:00 A.M.	102.2	128	26

TEMPERATURE, PULSE, AND RESPIRATION (*Cont'd*)

		T.	P.	R.
July 7	6:30 A.M.	102.6	128	26
	12:00 M.	103.4	132	28
	4:30 P.M.	103.4	130	28
	10:30 P.M.	102.8	132	28
July 8	2:00 A.M.			
	4:00 A.M.	100.4	126	28
	8:00 A.M.	100.4	114	28
	12:00 M.	102.2	120	28
	4:00 P.M.	101.6	126	32
	8:00 P.M.	102.	132	32
	12:00 P.M.	102.2	132	28
July 9	5:00 A.M.	101.	130	28
	8:00 A.M.	99.8	120	26
	12:00 M.	102.	136	32
	4:00 P.M.	101.4	120	34
	8:00 P.M.	101.8	130	34 (?)
	12:00 P.M.	99.8	127	34 (?)
July 10	4:30 A.M.	100.6	132	34
	8:00 A.M.	101.6	130	32
	12:00 M.	100.4	128	30
	4:00 P.M.	100.4	124	26
	8:00 P.M.	100.4	118	24
July 11	1:00 A.M.	101.	120	24
	4:00 A.M.	99.2	119	24
	8:00 A.M.			
	12:00 M.	100.	128	32
	4:00 P.M.	100.6	140	34
	8:00 P.M.	100.8		
	12:00 P.M.	99.4	120	22
July 12	4:00 A.M.	99.6	120	19
	8:00 A.M.	99.8	126	20
	12:00 M.	100.6	120	36
	4:00 P.M.	101.2	124	34
	8:00 P.M.	102.	124	33
	10:00 P.M.	99.4	118	22
July 13	12:30 A.M.	99.2	118	22
	5:00 A.M.	99.3	124	20
	12:00 M.	100.6	136	32
	1:00 P.M.	101.	134	30
	4:00 P.M.	101.	124	28
	8:00 P.M.	100.8	125	
July 14	1:00 A.M.	100.4	120	
	4:00 A.M.	100.	124	20
	8:00 A.M.	101.2	130	26
	3:00 P.M.	102.2	128	20
	4:00 P.M.	101.4	130	30
	8:00 P.M.	100.8	120	
	11:30 P.M.	100.6	118	22
July 15	4:00 A.M.	100.6	118	22
	8:00 A.M.	101.5	128	32
	12:00 M.	102.2	136	30
	4:00 P.M.	102.2	128	28
	8:00 P.M.	101.	125	28
July 16	12:30 A.M.	101.	129	31
	5:30 A.M.	100.8	125	27
	8:00 A.M.	100.6	136	28
	12:00 M.	100.4	124	32
	4:00 P.M.	101.	126	28
	8:00 P.M.	101.8	129	28
July 17	1:00 A.M.	100.	130	26
	5:00 A.M.	100.	132	32
	8:00 A.M.	101.	128	30
	12:00 M.	101.	130	28
	4:00 P.M.	101.6	128	28

TEMPERATURE, PULSE, AND RESPIRATION (*Cont'd*)

		T.	P.	R.
July 17	8:00 P.M.	101.	128	28
	12:00 P.M.	100.4	127	28
July 18	4:00 A.M.	99.	126	27
	8:00 A.M	100.8	130	30
	1:00 P.M.	101.3	126	28
	8:00 P.M.	101.2	130	28
	12:00 P.M.	100	134	36
July 19	4:00 A.M.	99.8	130	32
	8:00 A.M.	101.2	126	28
	12:00 M.	10.6	120	26
	4:00 P.M.	101.5	128	28
	8:30 P.M.	102.2	130	31
	11:00 P.M.	101.2	124	29
July 20	1:00 A.M.	101.4	124	28
	1:45 A.M	100.	122	30
	6:00 A.M.	100.4	124	26
	8:00 A.M.	100.6	120	22
	12:00 M.	99.8	120	20
	4:00 P.M.	101.6	128	26
	8:00 P.M.	101.8	88	24
	12:00 P.M.	100.6	128	26
July 21	4:00 A.M.	100.	128	24
	8:00 A.M.	99.8	116	22
	12:00 M.	100.6	120	26
	4:00 P.M.	101.3	124	22
	8:00 P.M.	100.8	124	24
	12:00 P.M.	100.	120	20
July 22	4:00 A.M.	100.	122	24
	8:00 A.M.	100.	120	22
	12:00 M.	100.	112	24
	4:00 P.M.	100.4	120	26
	8.00 P.M.	100.2	114	24
	12:00 P.M.	99.4	118	28
July 23	4:00 A.M.	98.3	120	26
	8:00 A.M.	100.2	116	24
	12:00 M.	99.8	124	24
	4:00 P.M.	100.	112	22
	8:00 P.M.	99.	116	30
	12:00 P.M.	99.6	120	30
July 24	4:00 A.M.	99.6	120	28
	8:00 A.M.	99.8	112	26
	12:00 M.	99.6	116	26
	4:00 P.M.	99.8	120	24
	8:00 P.M.	99.6	112	28
	12:00 P.M.	99.4	118	28
July 25	4:00 A.M.	99.8	124	22
	8:00 A.M.	101.4	124	24
	10:00 A.M.	101.8	128	24
	12:00 M.	102.	124	24
	4:00 P.M.	100.6	120	24
	8:00 P.M.	100.	120	24
	12:00 P.M.	99.6	118	24
July 26	4:00 A.M.	99.2	130	26
	8:00 A.M.	99.4	116	26
	12:00 M.	99.4	114	28
	4:00 P.M.	99.8	118	28
	8:00 P.M.	99.4	120	26
	12:00 P.M.	99.	110	22
July 27	4:00 A.M.	99.	120	22
	8:00 A.M.	99.	116	28
	12:00 M.	99.2	120	24
	4:00 P.M.	99.6	114	24
	8:00 P.M.	99.4	116	26
	12:00 P.M.	99.2	118	26
July 28	4:00 A.M.	98.6	120	20
	8:00 A.M.	99.	108	22
	12:00 M.	99.4	116	26

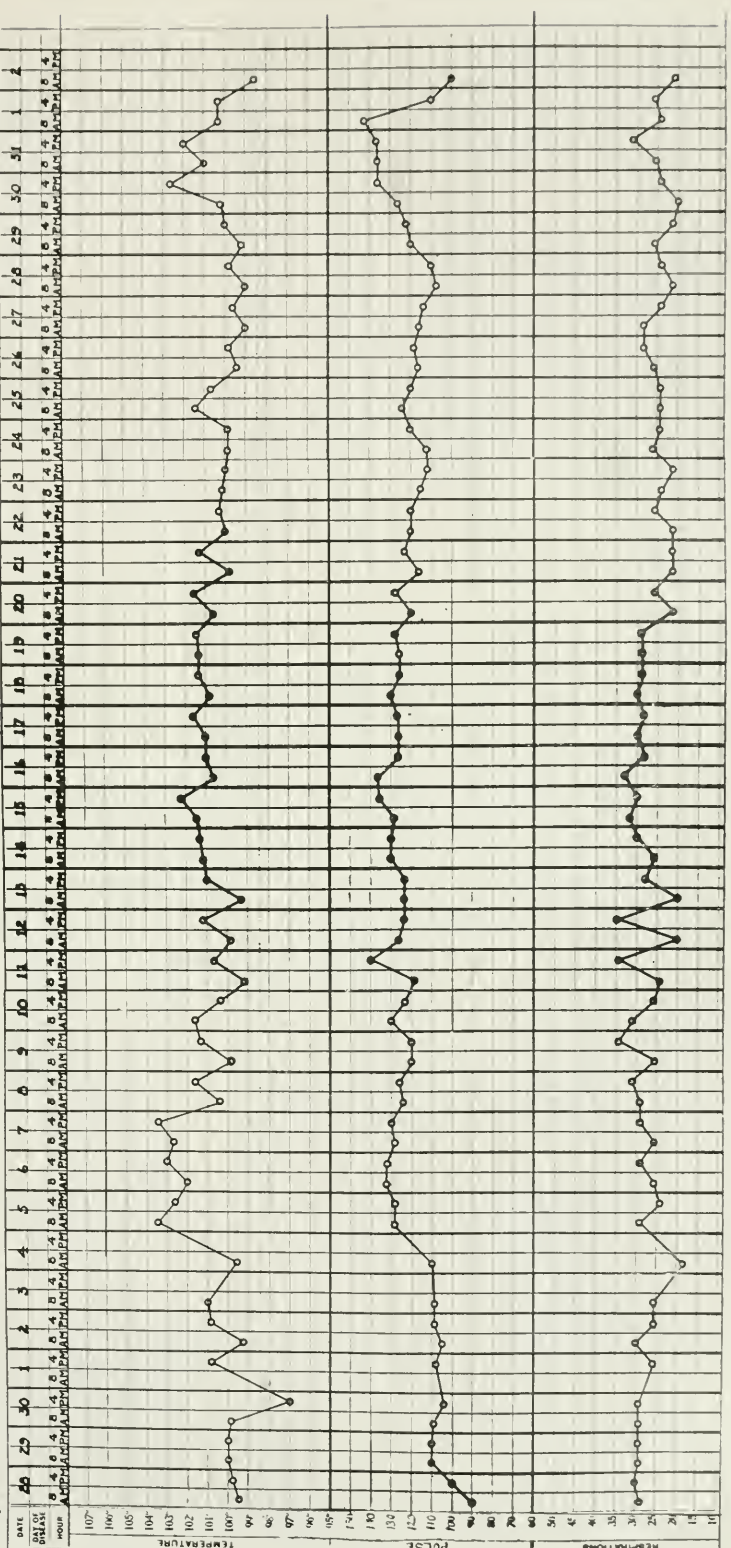
Typical Case No. III-Recovered
Case No.
Date
DATE
DAY OF DISEASE
HOUR
TEMPERATURE
PULSE
RESPIRATIONS

Chart 1.

TEMPERATURE, PULSE, AND RESPIRATION (*Cont'd*)

		T.	P.	R.
July 28	4:00 P.M.	99.8	110	24
	8:00 P.M.	99.4	120	20
	12:00 P.M.	99.4	116	22
July 29	4:00 A.M.	99.4	122	26
	8:00 A.M.	99.2	120	26
	12:00 M.	99.6	114	24
	4:00 P.M.			
	8:00 P.M.	100.	122	22
	12:00 P.M.	100.4	124	26
July 30	4:00 A.M.	99.4	116	22
	8:00 A.M.	100.2	126	20
	12:00 M.	101.6	132	24
	4:00 P.M.	102.6	136	24
	8:00 P.M.	101.8	136	28
	12:00 P.M.	100.4	136	28
July 31	4:00 A.M.	100.4	136	28
	8:00 A.M.	101.	136	26
	12:00 M.	101.6	130	32
	4:00 P.M.	102.	136	32
	7:00 P.M.	101.8	136	26
	8:00 P.M.	101.6	138	26
	12:00 P.M.	100.2	120	24
Aug. 1	4:00 A.M.	100.2	136	30
	8:00 A.M.	100.2	132	24
	12:00 M.	100.	118	22
	4:00 P.M.	100.2	110	26
	8:00 P.M.	99.6	110	24
	12:00 P.M.	98.6	100	22
Aug. 2	4:00 A.M.	98.6	100	24
	6:00 A.M.	98.6	100	26
	8:00 A.M.	98.6	100	22

(For graphic chart of temperature, pulse and respiration see Chart I.)

The further recovery was uneventful. The patient was discharged as completely cured about a month later.

BLOOD

	ERYTHROCYTE COUNT	WHITE COUNT	HEMOGLOBIN
July 10	4,650,000	24,600	75%
July 12	4,800,000	21,500	75%
July 14	.....	20,000	75%
July 16	.....	15,000	....
July 18	.....	15,000	....
July 20	.....	16.000	....
July 22	.....	15,700	....
July 24	.....	15,400	....
July 26	.....	15,500	....

Differential white counts two weeks, and four weeks after gassing.

	July 11	July 25
Polynuclears		
Neutrophile	86%	79.5%
Eosinophile	7%	2.0%
Basophiles	....	1.5%
Lymphocytes		
Large	....	1.0%
Small	1%	8.5%
Transitionals	....	.5%
Large basophilic mononuclears	2%	3.5%
Myelocytes, neutrophilic,	4%	3.5%

The platelets were increased, particularly in the earlier smears. There is an increase in the large deeply staining mononuclears. The red cells show no change and no nucleated red cells were found.

Urine and Blood Urea

Date	Fluid intake	Urine output amt. in 24 hrs.	Physical and chemical characteristics of the urine: Reaction	Specific gravity	Sugar glucose: Fehling's sol.	Albumin: Heller's HNO_3 ring test	Acidosis diacetic acid: Acetic ac. ferrocyanide	Renal functional efficiency: Ferric chloride	Quant. urea gm. per 100 c.c.	Quant. chloride gm. per 100 c.c.	Urea output in 24 hrs.	Chloride output in 24 hrs.	Diazo r.b.: Sulphanilic ac. Ehrlich's diazo	Dimethylaminobenzaldehyde	Pigment: Bromin water melanin	Gmelin's test for bile	Foam test for bile
July		c.c.									G						
8		1275	Acid	1025	Neg.	Pos.	Pos.	Neg.	—	0.06	—	0.765	—	—	—	Neg.	Neg.
9		1170	"	1025	Neg.	Pos.	Pos.	Neg.	—	0.48	—	5.6	—	—	—	Neg.	Neg.
10		1000	"	1025	Neg.	Pos.	Pos.	Neg.	0.40	0.10	4.00	1.0	—	—	—	Neg.	Neg.
11		1050	"	1017	Neg.	Pos.	Pos.	Neg.	—	0.10	—	1.05	Neg.	—	Neg.	Neg.	Neg.
FLUIDS FORCED																	
12		1870	"	1015	Neg.	Pos.	—	Neg.	0.59	0.06	—	1.12	Neg.	—	Neg.	Neg.	Neg.
13		1950	"	1014	Neg.	Pos.	—	Neg.	0.40	—	7.8	—	Neg.	—		Neg.	Neg.
14		1700	Slight	1017	Neg.	Pos.	—	Neg.	1.75	—	29.57	—	Neg.	Pos.		Neg.	Neg.
15			Acid	1015	Neg.	Pos.	—	Neg.	1.42	0.12	—	—	—	Pos.		Neg.	Neg.
16		550	"	1020	—	Pos.	—	—	0.52	0.12	—	—	—	Pos.	—	Neg.	Neg.
17		850	"	1027	—	Pos.	—	—	0.31	0.08	2.63	0.68	—	Pos.	—	Neg.	Neg.
18	3300	750	"	1027	—	Pos.	—	—	0.88	0.10	6.6	0.75	—	Pos.	—	Neg.	Neg.
19	2640	800	"	1025	—	Pos.	—	—	0.58	0.36	4.6	2.88	—	Pos.	—	Neg.	Neg.
20	3660	1400	"	1013	—	Pos.	—	—	—	0.20	—	2.80	—	Neg.	—	Neg.	Neg.
21	2640	1925	"	1009	—	Pos.	—	—	0.44	0.22	8.47	4.24	—	Neg.	—	Neg.	Neg.
22	3360	1650	"	1013	—	Pos.	—	—	—	0.26	—	4.29	—	Pos.	—	Neg.	Neg.
23	3360	1530	Amphoteric	1010	—	Trace	—	—	—	0.70	—	10.71	—	Neg.	—	Neg.	Neg.
24	2880	950	"	1022	—	Trace	—	—	—	0.80	—	7.6	—	—	—	—	—
25	2880	1750	"	1010	—	Trace	—	—	—	0.48	—	8.4	—	—	—	—	—
26	2640	2450	Neutral	1010	—	Trace	—	—	0.04	0.30	23.00	7.35	—	—	—	—	—
27	2160	2200	Slt. Ac.	1008	—	Trace	—	—	0.48	0.26	10.56	6.72	—	—	—	—	—
28	1920	1600	" "	1015	—	Neg.	Neg.	—	0.60	0.30			—	—	—	—	—
29	1920	2100	Neutral	1015	—	Neg.	Neg.	—	0.52	—	10.92	—	—	—	—	—	—
30	—	—	Slt. Ac.	1015	—	Trace	Trace	—	—	0.55	—	—	—	—	—	—	—
31	—	1900	" "	1012	—	Neg.	Neg.	—	—	—	—	—	—	—	—	—	—

BLOOD UREA

7/10 .060 Gm. per 100 c.c. blood.
28 .045 " " " " "

PHENOLSULPHONEPHTHALEIN

7/24 1st hr. plus 10 min. 1:00 to 2:10 50%
2nd " 2:10 to 3:10 No specimen obtainable.
Total..... 50%

At 3:30 15%.

SPUTUM

Mucopurulent, frothy, profuse in amount. More than usual number of streptococci, in chains of medium length.

CAST OF BRONCHUS

Pink flesh-like. Smears showed practically a mixed culture of rather medium short chained streptococci, Gram positive diplococci, and Gram negative large thick bacilli in chains.

	Color of urine	Urinary sediment
8	Transparent, red brown.	Very heavy shower of granular casts and peculiar split fiber casts. Leucocytes. Few red blood cells. Amorphous urates. Epithelial cells.
9	Translucent, red yellow.	
10	Lighter.	
11	Darker again.	Amorphous urates, granular casts, leucocytes and red blood cells.
FLUIDS FORCED		
12	Medium dark.	Excess amorphous urates. Uric acid. Few granular casts. Mucous cylindroids. Red blood cells.
13	" "	
14	Dark.	
15	"	
16	"	Somewhat improved. Amorphous urates. Leucocytes. Few hyaline and granular casts; renal and bladder epithelial cells.
17	"	Amorphous urates. Leucocytes, hyaline and fragments of granular casts. Red blood cells. Calcium oxalate crystals.
18	"	Abundant amorphous urates. Uric acid. Red and white blood cells. Few granular casts and epithelial cells.
19	Muddy.	Much improved. Few granular casts and epithelial cells. Few leucocytes. Bacteria.
20	Lighter.	Still improving. Amorphous urates. Few granular casts. Epithelial cells. Alkaline fermentation sediment with triple phosphates.
21	Slightly dark.	Abundant amorphous urates. Few red and white blood cells. Few granular casts and epithelial cells.
22	Darker.	Large amounts of sediment. Amorphous urates, granular epithelial cells. Few triple phosphates.
23	Lighter.	Amorphous urates. Few granular casts. Epithelial cells. Triple phosphates.
24	Normal.	Amorphous urates. Triple phosphates. Few granular epithelial cells

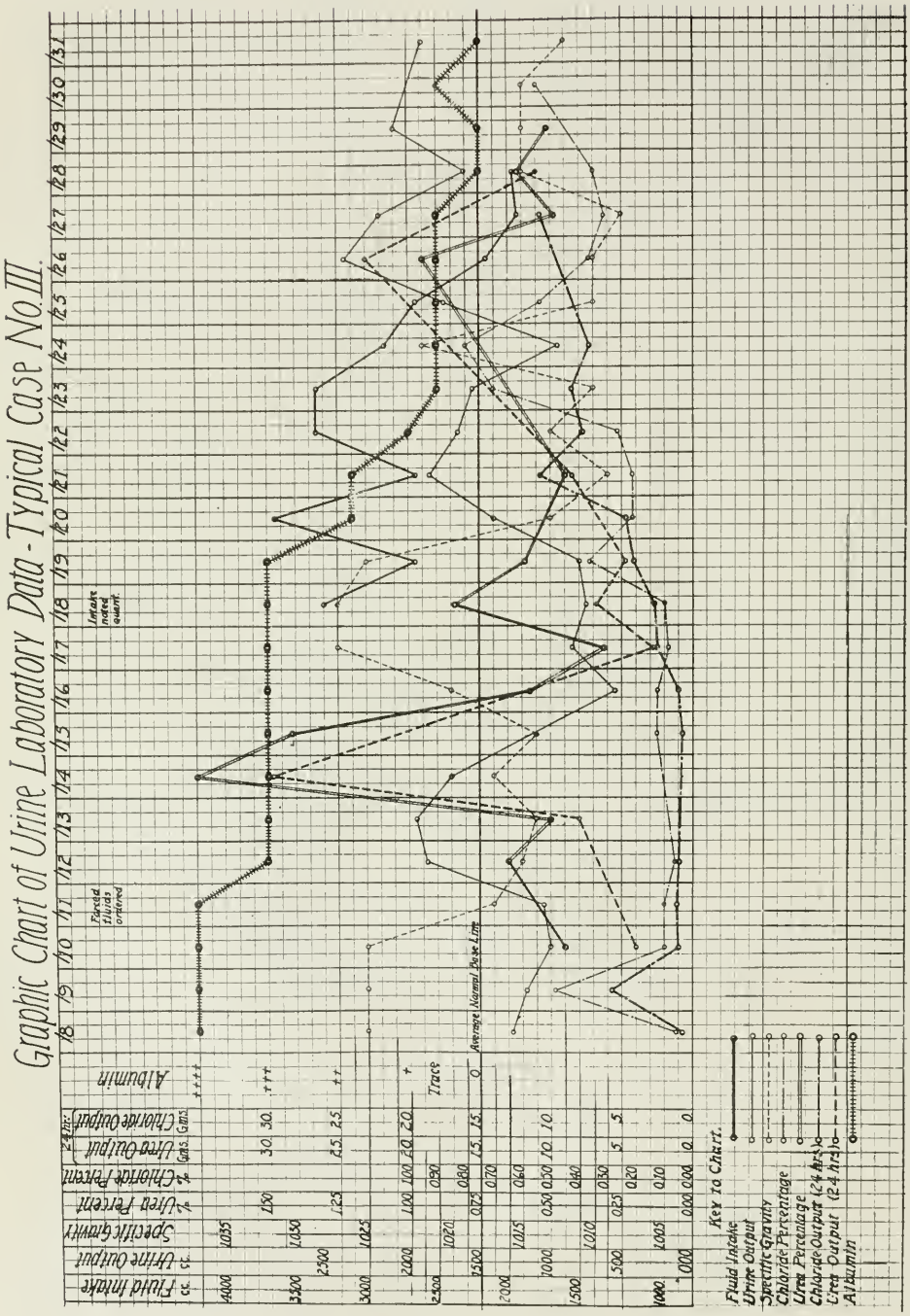
Graphic Chart of Urine Laboratory Data - Typical Case No. III.
Fluid Intake
Urine Output
Specific Gravity
Urea Percent
Chloride Percent
Urea Output
Chloride Output
Albumin
Forced fluids ordered
Intake noted quant.
Average Normal Base Line
Trace
Key to Chart.
Fluid Intake
Urine Output
Specific Gravity
Chloride Percentage
Urea Percentage
Chloride Output (24 hrs)
Urea Output (24 hrs)
Albumin

Chart II.

URINE AND BLOOD UREA (*Cont'd*)

	COLOR	SEDIMENT
25	Slightly dark.	Amorphous urates. Uric acid. Triple phosphates. Few granular leucocytes and epithelial cells.
26	Normal.	Slight sediment. Alkaline fermentation. Triple phosphates.
27	Medium dark.	Amorphous urates and triple phosphates.
28	Normal.	Amorphous urates and triple phosphates.
29	"	Much sediment, carbonates.
30	Sl. darker.	Few amorphous urates and triple phosphates. Few granular epithelial cells.
31	Normal.	Few granular epithelial cells, few leucocytes, otherwise normal.

(For graphic chart of the urinary changes, see Chart II.)

CASE IV.—This was a rather severe case of mustard gassing. The patient had extreme nausea and vomiting for five hours during the first night after being gassed. He developed severe genital lesions which became secondarily infected. There was also necrosis of the nasal and pharyngeal mucosa and some bronchitis.

TEMPERATURE, PULSE, AND RESPIRATION

		T.	P.	R.
July 4		Normal	Normal	Normal
July 5	8:00 A.M.	98.6	96	26
	4:00 P.M.	98.2	80	
July 6	4:00 A.M.	97.	80	18
	4:00 P.M.	98.6	96	18
July 7	6:00 A.M.	97.4	82	19
	8:00 A.M.			
	4:30 P.M.	99.	100	22
July 8	8:00 A.M.	97.4	92	22
	4:00 P.M.	97.6	94	22
July 9	4:00 P.M.	98.6	102	20
July 10	8:00 A.M.	97.6	100	24
	4:00 P.M.	98.6	98	20
July 11	4:00 P.M.	99.	112	24
July 12	4:00 P.M.	99.6	106	22
July 13	4:00 P.M.	100.	116	22
July 14	4:00 P.M.	100.	109	
July 15	8:00 A.M.	98.8	112	18
	4:00 P.M.	99.8	112	28
July 16	8:00 A.M.	98.8	86	
	4:00 P.M.	98.8	92	
July 17	7:30 A.M.	98.2	98	
	4:00 P.M.	98.8	78	
July 18	7:30 A.M.	100.	98	
	4:00 P.M.	99.8	88	
July 19	8:00 A.M.	98.8	80	
	4:00 P.M.	98.8	88	
July 20	7:30 A.M.	98.6	86	
	4:00 P.M.	99.	88	
July 21	7:30 A.M.	98.4	82	
	4:00 P.M.	99.	76	
July 22	7:30 A.M.	98.2	78	
	4:00 P.M.	98.8	82	
July 23	8:00 A.M.	98.6	78	20
	4:00 P.M.	98.6	98	20
July 24	8:00 A.M.	98.	80	18
	4:00 P.M.	98.6	112	20
July 25	8:00 A.M.	98.6	86	
	4:00 P.M.	98.8	88	
July 26	8:00 A.M.	98.6	80	
	4:00 P.M.	98.8	84	
July 27	8:00 A.M.	98.4	82	
	4:00 P.M.	98.6	86	
July 28	8:00 A.M.	98.	84	20
	4:00 P.M.	98.6	98	22
July 29	8:00 A.M.	98.2	86	18
	4:00 P.M.	98.6	98	

Urine and Blood Urea

	PHYSICAL AND CHEMICAL CHARACTERISTICS OF THE URINE			SUGAR GLUCOSE	ALBUMIN		ACIDOSIS DIACETIC ACID	RENAL FUNCTIONAL EFFICIENCY				DIAZO SUB.		PIGMENTS		
DATE	URINE OUTPUT AMT. IN 24 HRS.	REACTION	SPECIFIC GRAVITY	FEHLING'S SOL.	HELLER'S HNO_3 RING TEST	ACETIC AC. FERROCYANIDE	FERRIC CHLORIDE	QUANT. UREA GM. PER 100 C.C.	QUANT. CHLORIDE GM. PER 100 C.C.	UREA OUTPUT IN 24 HRS.	CHLORIDE OUTPUT IN 24 HRS.	SULPHANILIC AC. EHRLICH'S DIAZO	DIMETHYLAMINOBENZALDEHYDE UROBILINOGEN	BROMIN WATER MELANIN	GMELIN'S TEST FOR BILE	FOAM TEST FOR BILE
July	c.c.									G.	G.					
8	1000	Acid	1026	Neg.	Pos.	Pos.	Neg.	—	0.14	—	1.40	—	—	—	Neg.	Neg.
9	1000	"	1030	Neg.	Pos.	Pos.	Neg.	—	0.20	—	2.00	—	—	—	Neg.	Neg.
10	1600	"	1018	Neg.	Pos.	Pos.	Neg.	0.36	0.32	5.76	5.12	—	—	—	Neg.	Neg.
11	525	"	1023	Neg.	Pos.	Pos.	Neg.	—	0.26	—	1.36	Neg.	—	Neg.	Neg.	Neg.
12	1025	"	1020	Neg.	Pos.		Neg.	0.68	0.26	6.97	2.67	Neg.	—	Neg.	Neg.	Neg.
13	1600	"	1013	Neg.	Pos.		Neg.	0.62	—	9.92	—	Neg.	—	—	Neg.	Neg.
14	1100	Ampho-teric	1027	Neg.	Pos.		Neg.	2.56	—	28.16	—	Neg.	—	Neg.	Neg.	Neg.
15		Neutral	1015	—	Pos.		Neg.	1.22	0.20	—	—	—	Neg.	—	Neg.	Neg.
16	NO SPECIMEN COLLECTED															
17	350	Acid	1023	—	Pos.		Neg.	—	0.30	—	1.05	—	Neg.	—	Neg.	Neg.
18	1150	Neutral	1015	—	Pos.		—	0.67	0.80	7.60	9.20	—	Neg.	—	Neg.	Neg.
19	450?	Acid	1020	—	Neg.	Neg.	—	0.24	0.60	1.08	2.70	—	Neg.	—	Neg.	Neg.
20	650	"	1017	—	Neg.	Neg.	—	—	0.26	—	1.69					
21	540	"	1022	—	Pos.	Pos.	—	—	0.60	—	3.24	—	Neg.	—	Neg.	Neg.
22	1100	"	1019	—	Pos.	Pos.	—	—	0.58	—	6.38	—	Neg.	—	Neg.	Neg.
23	1075	Slight	1015	—	Neg.	Neg.	—	—	0.48	—	5.16	—	—	—	—	—
24	1000	"	1022	—	Neg.	Neg.	—	—	0.50	—	5.00	—	—	—	—	—
25	625	"	1017	—	Neg.	Neg.	—	—	0.38	—	3.62	—	—	—	—	—
26	1200	"	1022	—	Neg.	Neg.	—	1.05	0.58	1.80	6.96	—	—	—	—	—
27	800	"	1025	—	Pos.	Pos.	—	0.74	0.46	5.92	3.68	—	—	—	—	—
28	300	"	1023	—	Neg.	Neg.	—	0.72	0.66	2.16	1.98	—	—	—	—	—
29	500	"	1022	—	Neg.	Neg.	—	0.52	—	2.60	—	—	—	—	—	—

	BLOOD UREA		PHENOLSULPHONEPHTHALEIN TEST			
10	.0480 gm. per 100 c.c.	July 24	1st hr.	plus 10 min.	9:30 to 10:40	— 80
					10:40 to 11:40	— 10
					Total	90

	COLOR OF URINE	URINARY SEDIMENT
8	Medium lemon yellow. Turbid, heavy deposit.	Uric acid. Amorphous urates, crystals in showers. Cylindroids. Few granular casts. Epithelial cells.
9	Medium yellow, translucent.	
10	Straw color. Slightly turbid.	
11	Darker. Turbid.	Uric acid and amorphous urates in great showers. Few granular casts. Few white and red blood cells, few epithelial cells.
12	Normal.	Uric acid and amorphous urates. Otherwise negative.
13	Turbid.	
14	Dirty yellow.	
15	Normal.	
16	NO SPECIMEN COLLECTED.	
17	Medium dark, turbid.	Few uric acid and amorphous urates. Few triple phosphates and calcium oxalate. Few hyaline casts, renal and urethral epithelial cells. Numerous leucocytes.
18	Slightly dark, translucent.	Abundant uric acid and urates. Few triple phosphates, few granular epithelial casts.
19	Normal sediment.	Almost entirely amorphous urates. Few uric acid and few triple phosphates.
20	Normal.	Abundant amorphous urates, few uric acid, triple phosphates. Granular casts and granular epithelium.
21	Normal.	As above.
22	Normal.	As above but no casts noted.
23	Somewhat pale.	As above but no casts noted.
24	Normal.	As above but no casts noted.
25	Normal.	As above but no casts noted.
26	Normal.	Only triple phosphates and a few epithelial cells.
27	Medium dark.	As above.
28	Normal.	As above.
29	Normal.	Amorphous urates. Uric acid. Numerous leucocytes. Triple phosphates.

BLOOD

Examination of blood two weeks after gassing.

Erythrocyte count		4,500,000
White count		25,000,
Hemoglobin		76%
Differential white count:		
Polymuclears		
Neutrophile	84.0%	
Eosinophile	1.5%	
Lymphocytes		
Large	2.0%	
Small	3.0%	
Transitionals	.5%	
Large basophilic mononuclears	1.5%	
Myelocytes, neutrophilic,	7.5%	

The blood platelets were increased. There were no changes in the red cells.

CASE V.—This patient had severe mustard gas burns about the genitals, in the axillæ and at the bends of the elbows. There was a less severe generalized burn. A marked generalized secondary furunculosis complicated the later course of this patient.

TEMPERATURE, PULSE, AND RESPIRATION

		T.	P.	R.
June 27	7:30 P.M.	97.6	112	26
June 28		98.2	110	24
June 29				
June 30		98.6	90	
July 1		99.	82	
July 2		98.8	90	
July 3	5:00 P.M.	98.8	97	
July 4	6:00 A.M.	98.4	110	
July 5	4:00 P.M.	100.	108	
July 6	4:00 A.M.	98.	102	22
	4:00 P.M.	99.2	116	22
July 7	4:00 A.M.	98.	108	22
	4:00 P.M.	98.6	104	22
July 8	2:45 A.M.			
	4:00 A.M.	97.	110	
	4:00 P.M.	99.6	112	18
July 9	4:00 A.M.	98.8	98	20
July 10	8:00 A.M.	96.8	112	16
	4:00 P.M.	99.4	112	24
July 11	4:00 P.M.	99.	110	22
July 12	4:00 P.M.	99.4	106	22
July 13	4:00 P.M.	100.6	102	20
July 14	7:30 P.M.	102.	110	
July 15	8:00 A.M.	99.	100	18
	12:00 M.	98.8	100	18
	4:00 P.M.	100.	112	26
	7:30 P.M.			
July 16	8:00 A.M.	98.6	88	
	4:00 P.M.	98.6	92	
July 17	7:30 A.M.	98.2	88	
	4:00 P.M.	98.	82	
July 18	7:30 A.M.	98.2	88	
	4:00 P.M.	98.2	84	
July 19	8:00 A.M.	97.8	80	
	4:00 P.M.	98.	78	
July 20	7:30 A.M.	97.6	68	
	4:00 P.M.	98.4	76	
July 21	8:00 A.M.			
	4.00 P.M.	98.8	78	

TEMPERATURE, PULSE, AND RESPIRATION (*Cont'd*)

		T.	P.	R.
July 22	7:30 A.M.	97.8	76	
	4:00 P.M.	98.6	80	
July 23	8:00 A.M.	98.	68	
	4:00 P.M.	98.2	76	
July 24	8:00 A.M.	97.	74	
	4:00 P.M.	98.6	82	
July 25	8:00 A.M.	97.6	68	
	4:00 P.M.	99.	78	
July 26	8:00 A.M.	97.8	78	
	4:00 P.M.	98.8	78	
July 27	8:00 A.M.	98.	76	
	4:00 P.M.	98.6	78	
July 28	8:00 A.M.	97.4	70	18
July 29	8:00 A.M.	98.2	68	18
	4:00 P.M.	98.	80	20

URINE AND BLOOD UREA

	PHYSICAL AND CHEMICAL CHARACTERISTICS OF THE URINE			SUGAR GLUCOSE	ALBUMIN	ACIDOSIS DIACETIC ACID		RENAL FUNCTIONAL EFFICIENCY				DIAZO SUB.		PIGMENTS		
DATE	URINE OUTPUT AMT. IN 24 HRS.	REACTION	SPECIFIC GRAVITY	FEHLING'S SOL.	HELLER'S HNO_3 RING TEST	ACETIC AC. FERROCYANIDE	FERRIC CHLORIDE	QUANT. UREA GM. PER 100 C.C.	QUANT. CHLORIDE GM. PER 100 C.C.	UREA OUTPUT IN 24 HRS.	CHLORIDE OUTPUT IN 24 HRS.	SULPHANILIC AC. EHRLICH'S DIAZO	DIMETHYLAMINOBENZALDEHYDE UROBILINOGEN	BROMIN WATER MELANIN	GMELIN'S TEST FOR BILE	FOAM TEST FOR BILE
July	c.c.															
8	1350	Acid	1026	Neg.	Pos.	Pos.	Neg.	—	0.56	—	7.56	—	—	—	Neg.	Neg.
9	500	"	1026	Neg.	Pos.	Pos.	Neg.	—	0.64	—	3.20	—	—	—	Neg.	Neg.
10	950	"	1022	Neg.	Pos.	Pos.	Neg.	0.49	0.28	4.65	7.66	—	—	—	Neg.	Neg.
11	600	"	1022	Neg.	Pos.	Pos.	Neg.	—	0.06	—	0.36	Neg.	—	Neg.	Neg.	Neg.
12	900	Slight	1018	Neg.	Pos.	Pos.	Neg.	0.40	0.30	3.60	2.70	Neg.	—	Neg.	Neg.	Neg.
13	970	Acid	1020	Neg.	Pos.	Pos.	Neg.	0.73	—	7.08	—	—	—	—	Neg.	Neg.
14	850	"	1025	Neg.	Pos.	Pos.	Neg.	1.26	—	10.71	—	Neg.	—	Neg.	Neg.	Neg.
15	—	Slight	1025	Neg.	Trace	—	Neg.	1.61	0.34	—	—	—	—	—	Neg.	Neg.
16	675	Acid	1015	Neg.	Pos.	—	Neg.	0.40	0.34	2.70	2.30	—	—	Neg.	Neg.	Neg.
17	1425	"	1013	Neg.	Trace	—	Neg.	—	0.52	—	7.41	—	Neg.	—	Neg.	Neg.
18	700	"	1023		Neg.	Neg.	Neg.	0.44	0.78	3.08	5.46	—	Neg.	—	Neg.	Neg.
19	750	"	1025	—	Neg.	Neg.	—	0.52	0.86	3.90	6.54	—	Neg.	—	Neg.	Neg.
20	1100	"	1010	—	Neg.	—	—	—	0.38	—	4.18	—	Neg.	—	Neg.	Neg.
21	620	"	1024	—	Neg.	—	—	—	0.48	—	2.97	—	—	—	Neg.	Neg.
22	1100	"	1010	—	Neg.	—	—	—	0.62	—	6.82	—	Neg.	—	Neg.	Neg.
23	1625	"	1010	—	Neg.	—	—	—	0.54	—	8.77	—	—	—	Neg.	Neg.
24	1400	"	1012	—	Neg.	—	—	—	0.72	—	10.08	—	—	—	Neg.	Neg.
25	1000	"	1010	—	Neg.	—	—	—	0.76	—	7.60	—	—	—	Neg.	Neg.
26	2100	"	1013	—	Neg.	—	—	0.72	0.60	15.12	12.60	—	—	—	Neg.	Neg.
27	1600	Slight	1015	—	Neg.	—	—	0.67	0.60	10.72	9.60	—	—	—	Neg.	Neg.
28	2000	"	1015	—	Neg.	—	—	0.50	0.50	10.00	10.00	—	—	—	Neg.	Neg.
29	1400	"	1015	—	—	—	—	—	—	—	—	—	—	—	—	—

BLOOD UREA

Blood unobtainable.

PHENOLSULPHONEPHTHALEIN TEST

July 24 1st hour plus 10 min. 70% excreted.
2nd hour 15% "

Total.....85%

Smears from furuncles and hordeolum showed only pus and staphylococci.

COLOR OF URINE

8 Medium lemon yellow, cloudy.

9 Medium lemon yellow, translucent.

11 Darker.

12

13 Medium dark.

14 Dark.

URINARY SEDIMENT

Uric acid and amorphous urates. Few casts and cylindroids, granular and hyaline casts, epithelial squamous cells with large golden yellow droplets, markedly refractive. Fatty degeneration.

As above plus calcium oxalate crystals. Fragments of granular casts.

As above. Crystals in excess. Few red blood cells, few leucocytes, few granular casts.

URINE AND BLOOD UREA (*Cont'd*)

	COLOR OF URINE	URINARY SEDIMENT
15	Normal.	Sediment much improved.
16	Medium dark.	Few fragments of granular casts. Epithelial cells, leucocytes and amorphous urates.
17	Pale.	As above plus few red blood cells.
18	Normal	Uric acid, amorphous urates, calcium oxalate. Few red and white blood cells. Few granular epithelial cells.
19	Normal.	Abundant uric acid, as above.
20	Normal.	As above.
21	Slightly pale.	As above.
22	Normal.	As above.
23	Slightly pale.	As above and a few granular casts.
24	Slightly pale.	As above
25	Normal.	Improved, only a few urates and a few granular epithelial cells were found.
26	Pale.	As next above.
27	Pale.	As next above.
28	Normal.	As next above.
29	Normal.	As next above.

BLOOD

Examination of blood sixteen days after gassing.

Erythrocyte count		4,600,000
White count		21,200
Hemoglobin		78%
Differential white count:		
Polynuclears		
Neutrophile	92. %	
Eosinophile	1.5%	
Basophile	.5%	
Lymphocytes		
Large	2.0%	
Small	2.0%	
Transitionals	1.0%	
Large mononuclears, none found		
Myelocytes	1.0%	

The polymorphonuclears show the Arneth scale to the right, older polynuclears. The platelets are greatly increased in number. Many of the red cells are undersized. No nucleated red cells were found.

CASE VI.—In this case there were severe genital burns which developed a severe secondary pyogenic infection. The general skin involvement was less severe, but well marked.

BLOOD

Examination of blood two weeks after gassing.

Erythrocyte count		4,860,000
White count		16,600
Hemoglobin		78%
Differential white count:		
Polynuclears		
Neutrophile	66 %	
Eosinophile	4.5%	
Lymphocytes		
Large	3.0%	
Small	7.5%	
Transitionals	1.5%	
Large basophilic mononuclears	5.5%	
Myelocytes	12.0%	

The blood platelets are increased. There are no changes in the red cells. No nucleated red cells were found.

URINE AND BLOOD UREA

	PHYSICAL AND CHEMICAL CHARACTERISTICS OF THE URINE			SUGAR GLUCOSE	ALBUMIN		ACIDOSIS DIACETIC ACID	RENAL FUNCTIONAL EFFICIENCY				DIAZO SUB.		PIGMENTS		
DATE	URINE OUTPUT AMT. IN 24 HRS.	REACTION	SPECIFIC GRAVITY	FEHLING'S SOL.	HELLER'S HNO_3 RING TEST	ACETIC AC. FERROCYANIDE	FERRIC CHLORIDE	QUANT. UREA GM. PER 100 C.C.	QUANT. CHLORIDE GM. PER 100 C.C.	UREA OUTPUT IN 24 HRS.	CHLORIDE OUTPUT IN 24 HRS.	SULPHANILIC AC EHRLICH'S DIAZO	DIMETHYLAMINOBENZALDEHYDE UROBILINOGEN	BROMIN WATER MELANIN	GMELIN'S TEST FOR BILE	FOAM TEST FOR BILE
July	c.c.															
8	460	Acid	1024	Neg.	Pos.	Pos.	Neg.	—	0.16	—	0.82	Neg.	—	Neg.	Neg.	Neg.
9	750	"	1015	Neg.	Pos.	Pos.	Neg.	—	0.30	—	2.25	—	—	—	Neg.	Neg.
10	1150	"	1015	Neg.	Pos.	Pos.	Neg.	0.38	0.14	4.38	1.61	Neg.	—	Neg.	Neg.	Neg.
11	620	Mark	1024	Neg.	Pos.	Pos.	Neg.	—	0.38	—	7.45	—	—	—	Neg.	Neg.
12	630	Acid	1024	Neg.	Trace	Trace	Neg.	0.58	1.16	3.65	7.31	—	—	—	Neg.	Neg.
13	300?	"	1018	Neg.	Trace	Trace	Neg.	0.36	—	1.08	—	—	—	—	Neg.	Neg.
14	900	"	1020	Neg.	Pos.	Pos.	Neg.	1.56	—	14.04	—	Neg.	—	Neg.	Neg.	Neg.
15	NO SAMPLE															
16	NO SAMPLE															
17	1600	Acid	1018	Neg.	Pos.	Pos.	Neg.	—	0.40	—	6.40				Neg.	Neg.
18	LEFT THE INFIRMARY.															

BLOOD UREA

Blood unobtainable.

PHENOLSULPHONEPHTHALEIN TEST

Patient left before the apparatus was secured.

	COLOR OF URINE	URINARY SEDIMENT
3	Turbid. Deep lemon yellow.	Amorphous urates and uric acid crystals in showers. Few leucocytes. Few hyaline casts.
9	Light lemon, cloudy.	
10	Lighter.	
11	Darker again.	As above plus calcium oxalate crystals, in great numbers. Granular as well as hyaline casts. Epithelial cells, both renal and bladder.
12	Normal.	As above except no casts were noted.
13	Normal.	
14	Lighter, normal.	
15	Normal.	
16	Normal.	
17	Normal.	Few uric acid and amorphous urates. Few fragments of granular casts. Few red and white blood cells.
18	Normal.	

CASE VII.—Comparatively mild case of mustard gassing. Slight burns of genitals, axillæ and in the bends of the elbows. General erythema of skin over entire body.

BLOOD

Examination of blood two weeks after gassing.

Erythrocyte count		5,300,000
White count		19,500
Hemoglobin		100%
Differential white count		
Polynuclears		
Neutrophiles	71.5%	
Eosinophiles	5.5%	
Lymphocytes		
Large	3.5%	
Small	10.5%	
Transitionals	.5%	
Large basophilic mononuclears	6.0%	
Myelocytes	2.5%	

There is an increase in the normal granular mononuclears. The blood platelets are increased. No nucleated reds, or other changes in the red cells, were found.

Urine and Blood Urea

	PHYSICAL AND CHEMICAL CHARACTERISTICS OF THE URINE			SUGAR GLUCOSE	ALBUMIN		ACIDOSIS DIACETIC ACID	RENAL FUNCTIONAL EFFICIENCY				DIAZO SUB.	PIGMENTS			
DATE	URINE OUTPUT AMT. IN 24 HRS.	REACTION	SPECIFIC GRAVITY	FEHLING'S SOL.	HELLER'S HNO_3 RING TEST	ACETIC AC. FERROCYANIDE	FERRIC CHLORIDE	QUANT. UREA GM. PER 100 C.C.	QUANT. CHLORIDE GM. PER 100 C.C.	UREA OUTPUT IN 24 HRS.	CHLORIDE OUTPUT IN 24 HRS.	SULPHANILIC AC. EHRLICH'S DIAZO	DIMETHYLAMINOBENZALDEHYDE UROBILINOGEN	BROWN WATER MELANIN	GMELIN'S TEST FOR BILE	FOAM TEST FOR BILE
July	c.c.															
8	575	Acid	1026	Neg.	Pos.?	Pos.?	Neg.	—	0.82	—	4.62	—	—	—	Neg.	Neg.
9	1000	"	1027	Neg.	Pos.	Pos.	Neg.	—	0.52	—	5.20	—	—	—	Neg.	Neg.
10	1000	"	1027	Neg.	Pos.?	Pos.?	Neg.	0.38	0.14	3.80	1.40	—	—	—	Neg.	Neg.
11	900	"	1020		Pos.	Pos.	Neg.	—	0.12	—	1.08	Neg.	—	Neg.	Neg.	Neg.
12	1450	"	1019	Neg.	Neg.	Neg.	Neg.	0.54	0.34	7.83	4.93	Neg.	—	Neg.	Neg.	Neg.
13	250?	"	1027	Neg.	Pos.	Pos.		1.12	—	2.80?	—	Neg.	—	Neg.	Neg.	Neg.
14	600	"	1025	Neg.	Pos.	Pos.	Neg.	2.26	—	13.56	—	Neg.	—	Neg.	Neg.	Neg.
15	—	"	1025	Neg.	Neg.	Neg.	Neg.	1.32	0.80	—	—	—	Neg.	—	Neg.	Neg.
16	NO SAMPLE															
17	400?	"	1023		Neg.	—	Neg.	—	0.52	—	2.08?	—	Neg.	—	Neg.	Neg.
18	900	Neut.	1025		Pos.	Pos.	Neg.	0.48	0.54	4.32	4.86	—	Neg.	—	Neg.	Neg.
19	600	Acid	1025		Neg.	Neg.		0.48	0.86	2.88	4.56	—	Neg.	—	Neg.	Neg.
20	550	"	1025		Neg.	Neg.	—	—	0.30	—	1.65	—	Neg.	—	Neg.	Neg.
21	590	"	1027		Trace	Trace	—	—	0.20	—	1.18	—	Neg.	—	Neg.	Neg.
22	900	"	1017		Trace	Trace	—	—	0.38	—	3.42	—	Neg.	—	Neg.	Neg.
23	565	"	1024		Neg.	Neg.	—	—	0.70	—	4.65	—	Neg.	—	Neg.	Neg.
24	500	"	1025		Neg.	Neg.	—	—	0.72	—	3.60	—	—	—	Neg.	Neg.
25	LEFT THE HOSPITAL.															

BLOOD UREA

July 10 .0264 Gm. per 1000 c.c. of blood

PHENOLSULPHONEPHTHALEIN

1st hr. plus 10 min. 60% excreted.
2nd hr. 20% "
Total.....80% "

URINARY SEDIMENT

8 Few amorphous urates and uric acid crystals. Few cylindroids and granular casts. Few epithelial cells.

11 Amorphous urates. Few uric acid crystals and calcium oxalate crystals. Few hyaline and granular casts and cylindroids. Leucocytes and a few red blood cells and epithelial cells.

12 Few amorphous urates. Few squamous epithelial cells, otherwise normal.

17 Abundant amorphous urates, few uric acid crystals. Few leucocytes and granular epithelial cells.

18 Sediment crystalline in character. Abundant uric acid and urates, numerous calcium oxalate crystals. Few leucocytes and granular epithelial cells.

19 Few amorphous urates and uric acid and calcium oxalate crystals.

20 Abundant amorphous urates, uric acid and calcium oxalate. Triple phosphates. Few leucocytes. Few granular epithelial cells.

21 Few amorphous urates, uric acid, calcium oxalate; few hyaline and few fragments of blood casts. Few granular epithelial cells.

22 Amorphous urates. Few calcium oxalates and triple phosphates.

23 Excess of amorphous urates and triple phosphates, otherwise negative.

Case VIII.—Mild case. Recovery.

Urine and Blood Urea

	PHYSICAL AND CHEMICAL CHARACTERISTICS OF THE URINE		SUGAR GLUCOSE	ALBUMIN	ACIDOSIS DIACETIC ACID		RENAL FUNCTIONAL EFFICIENCY				DIAZO SUB.		PIGMENTS		
DATE	URINE OUTPUT AMT. IN 24 HRS.	REACTION	SPECIFIC GRAVITY	FEHLING'S SOL.	HELLER'S HNO_3 RING TEST	ACETIC AC. FERROCYANIDE	FERRIC CHLORIDE	QUANT. UREA GM. PER 100 C.C.	QUANT. CHLORIDE GM. PER 100 C.C.	UREA OUTPUT IN 24 HRS.	CHLORIDE OUTPUT IN 24 HRS.	SULPHANILIC AC. EHRLICH'S DIAZO	DIMETHYLAMINOBENZALDEHYDE UROBILINOGEN	BROMIN WATER MELANIN	GMELIN'S TEST FOR BILE	FOAM TEST FOR BILE
July	c.c.															
8	585?	Acid	1030	Neg.	Pos.?	Pos.	Neg.	—	0.22	—	1.28	—	—	—	Neg.	Neg.
9	450?	"	1025	Neg.	Pos.	Pos.	Neg.	—	0.22	—	.99	—	—	—	Neg.	Neg.
10	950	"	1017	Neg.	Pos.	Pos.	Neg.	0.25	0.36	2.37	3.42	—	—	—	Neg.	Neg.
11	500?	"	1023		Pos.	Pos.	Neg.	—	0.40	—	2.00	Neg.	—	Neg.	Neg.	Neg.
12	1125	"	1015	Neg.	Trace	Trace	Neg.	0.43	0.38	4.83	4.27	Neg.	—	Neg.	Neg.	Neg.
13	—	"		Neg.				0.78	—	—	—					
14	920	Alk.	1025	Neg.	Pos.	Pos.	Neg.	0.12	—	1.10	—	Neg.	—	Neg.	Neg.	Neg.
15	NO SAMPLES SUBMITTED AFTER THE ABOVE EXAMINATIONS.															

BLOOD UREA. .0312 G per 100 c.c. NO FURTHER DATA OBTAINABLE.

8 URINARY SEDIMENT Calcium oxalate crystals. Few granular casts and cylindroids. Epithelial cells and leucocytes.

11 Amorphous urates. Small granular casts. Many epithelial cells (renal and bladder type). Few red and white blood cells.

12 Excess of amorphous urates, few uric acid, few granular casts. Red blood cells? Granular bladder epithelial cells.

Blood

Hemoglobin. 75 per cent. No other examination made.

Case IX.—Mild case. Recovery.

Temperature, Pulse, and Respiration

		T.	P.	R.
July 11		Normal		
July 12		Normal		
July 13		Normal		
	4:00 P.M.	97.6	76	
July 14		Normal		
July 15		Normal		
July 16	8:30 A.M.	98.4	78	
	4:00 P.M.	98.8	80	
July 17	7:30 A.M.	98.	76	
	4:00 P.M.	98.6	88	
July 18	7:30 A.M.	98.2	78	
	4:00 P.M.	98.2	74	
July 19	8:00 A.M.	98.	78	
	4:00 P.M.	98.4	79	
July 20	7:30 A.M.	98.	76	
	4:00 P.M.	98.6	80	
July 21	7:30 A.M.	97.8	70	
July 22	7:30 A.M.	98.	80	
	4:00 P.M.	98.6	82	

TEMPERATURE, PULSE, AND RESPIRATION (*Cont'd*)

		T.	P.	R.
July 23	8:00 A.M.	98.	68	
	4:00 P.M.	98.	80	18
July 24	8:00 A.M.	98.	80	18
	4:00 P.M.		84	20
July 25	8:00 A.M.	98.	76	18
	4:00 P.M.	98.6	82	
July 26	8:00 A.M.	98.	78	
	4:00 P.M.	98.	82	
July 27	8:00 A.M.	98.	80	
	4:00 P.M.	98.6	80	
July 28	8:00 A.M.	97.8	76	
	4:00 P.M.	98.6	76	
July 29	8:00 A.M.			
	4:00 P.M.	98.4	74	

URINE AND BLOOD UREA

	PHYSICAL AND CHEMICAL CHARACTERISTICS OF THE URINE			SUGAR GLUCOSE	ALBUMIN	ACIDOSIS DIACETIC ACID		RENAL FUNCTIONAL EFFICIENCY				DIAZO SUB.	PIGMENTS			
DATE	URINE OUTPUT AMT. IN 24 HRS.	REACTION	SPECIFIC GRAVITY	FEHLING'S SOL.	HELLER'S HNO_3 RING TEST	ACETIC AC. FERROCYANIDE	FERRIC CHLORIDE	QUANT. UREA GM. PER 100 C.C.	QUANT. CHLORIDE GM. PER 100 C.C.	UREA OUTPUT IN 24 HRS.	CHLORIDE OUTPUT IN 24 HRS.	SULPHANILIC AC. EHRLICH'S DIAZO	DIMETHYLAMINOBENZALDEHYDE UROBILINOGEN	BROMIN WATER MELANIN	GMELIN'S TEST FOR BILE	FOAM TEST FOR BILE
July	c.c.															
17	550	Acid	1024	Neg.	Neg.	Neg.	Neg.	—	0.58	—	3.19	Neg.	Neg.	Neg.	Neg.	Neg.
18	650	"	1018	Neg.	Neg.	Neg.	Neg.	0.49	0.70	3.18	4.55	—	Neg.	—	Neg.	Neg.
19	1100	"	1015	Neg.	Neg.	Neg.	Neg.	0.32	0.60	3.52	6.60	—	Neg.	—	Neg.	Neg.
21	1050	"	1015	—	Neg.	Neg.	Neg.	—	0.78	—	8.19	—	Neg.	—	Neg.	Neg.
22	500	Neut.	1017	—	Neg.	Neg.	Neg.	—	0.58	—	2.90	—	Neg.	—	Neg.	Neg.
23	820	"	1017	—	Neg.	Neg.	Neg.	—	0.34	—	2.78	—	—	—	—	—
24	1850	Acid	1012	—	Neg.	Neg.	Neg.	—	0.70	—	12.95	—	—	—	—	—
25	1150	"	1013	—	Neg.	Neg.	Neg.	—	0.38	—	4.37	—	—	—	—	—
26	700		1025	—	Neg.	Neg.	Neg.	1.6	0.36	11.20	2.52	—	—	—	—	—
27	1050		1015		Neg.	Neg.		0.72	0.70	7.56	7.35	—	—	—	—	—
28	400?	Acid	1023		Neg.	Neg.		0.84	0.66	3.33	2.64	—	—	—	—	—
29	700	"	1017		Neg.	Neg.		—	—	—	—	—	—	—	—	—

PHENOLSULPHONEPHTHALEIN TEST

1st hr. plus 10 min. 60% excreted.
2nd hr. 10% "
Total..... 70% "

URINARY SEDIMENT

17 Few amorphous u[illegible]s, few leucocytes, few red and white blood cells, few granular epithelial cells.
18 Crystalline in character consisting largely of uric acid and amorphous urates. Otherwise normal.
19 Excess of uric acid and amorphous urates. Otherwise negative.
21 Abundant amorphous urates. Otherwise negative.
22 Crystalline. Large amounts amorphous urates. Some triple phosphates, otherwise negative.
23 As on previous day, less in amount.
24 As on previous day, still less in amount.
25 Excess amorphous urates, triple phosphates, otherwise negative.
26 As next above.

CASE GROUP X.—All mild cases with recovery.

TEMPERATURE, PULSE, AND RESPIRATION

		T.	P.	R.
CASE X-A				
July 27	8:00 A.M.	97.8	68	
	4:00 P.M.	98.4	74	
July 28	8:00 A.M.	97.8	68	
	4:00 P.M.	98.8	76	20
July 29	8:00 A.M.	97.	68	18
	4:00 P.M.	98.2	80	
CASE X-B				
July 22	7:30 A.M.	97.8	78	
	4:00 P.M.	98.4	80	
July 23	8:00 A.M.	97.6	72	
July 24	8:00 A.M.	97.	76	
	4:00 P.M.	98.6	78	
July 25	8:00 A.M.	97.6	78	
	4:00 P.M.	98.6	78	
July 27	8:00 A.M.	98.4	74	
July 28	8:00 A.M.	97.	68	
July 29	8:00 A.M.	Normal		
	4:00 P.M.	98.	76	
CASE X-C				
July 23	10:00 P.M.	97.6	70	19
July 24	8:00 A.M.	97.6	74	20
	4:00 P.M.	98.2	76	20
July 25	8:00 A.M.	98.	74	18
	4:00 P.M.	98.	74	
July 26	8:00 A.M.	97.8	74	
	4:00 P.M.	98.	76	
July 27	8:00 A.M.	97.8	74	
	4:00 P.M.	98.4	74	
July 28	8:00 A.M.	97.4	76	18
	4:00 P.M.	98.6	80	20
July 29	8:00 A.M.	97.6	76.	
	4:00 P.M.	98.2		
CASE X-D		Normal	Normal	Normal

URINE AND BLOOD UREA

PHYSICAL AND CHEMICAL CHARACTERISTICS OF THE URINE					ALBUMIN						
	REACTION	SPECIFIC GRAVITY	FEHLING'S SOL.	HELLER'S HNO_3 RING TEST	ACETIC AC. FERROCYANIDE	HEAT AND NITRIC ACID	HEAT AND ACETIC ACID	PER CENT CHLORIDE GM. PER 100 C.C.	COLOR	SEDIMENT	
A.*	Acid	1022	Neg.	Neg.	Neg.	Neg.	Neg.	0.38	Clear Normal.	Negative.	
B.**	"	1020	Neg.	Neg.	Neg.	Neg.	Neg.	0.54	Clear-Normal.	Negative.	
C.***	"	1020	Neg.	Neg.	Neg.	Neg.	Neg.	0.78	"	"	"
D.****	"	1030	Neg.	Neg.	Neg.	Neg.	Neg.	0.56	"	"	Numerous leucocytes, otherwise negative.

PHENOLSULPHONEPHTHALEIN TEST

A.	10 min. plus 1st hr.	60% excreted.	2nd hr. 15%.	Total 75%.
B.	10 min. plus 1st hr.	50% excreted.	2nd hr. 30%.	Total 80%.
C.	10 min. plus 1st hr.	55% excreted.	2nd hr. 20%.	Total 75%.

NOTE.—These were all comparatively mild cases, and they were used more or less as controls.

*A. Had had large burns of the feet and smaller ones of the hands. His face was erythematous and his eyes showed acute congestion on the more or less chronic conjunctivitis.
**B. Had had severe hand burns, and a very intense conjunctivitis.
***C. Had had a chronic mild conjunctivitis, and an aphonia.
****D. Had no signs of irritation.

BLOOD: These cases showed no blood changes.

GENERAL DISCUSSION OF THE RESULTS

The chemical and microscopic laboratory examinations were carred out as completely as was possible and the negative results were charted as well as the positive pathologic findings. The negative results will serve not only as a guarantee that the specific examinations have been made, but will also furnish a broader basis for further work along this line. Some reactions were found to be negative throughout the series of cases. Fehling's solution failed to reveal any glucose or other reducing substance in these urines. The dilute ferric chloride test never gave the heat labile Burgundy-red reaction of diacetic acid, and on this basis a definite acidosis is ruled out. Of course we can not conclude anything concerning the height of the alkali reserve of the blood from this finding. It may be, and probably is, quite low as we may roughly conclude from the markedly acid urinary reaction and the sediment. Ehrlich's sulphanilic-hydrochloric acid and sodium nitrite reaction for diazo substances was found to be negative in every instance. No melanin reaction was ever noted in the several bromine water oxidizing tests for the pigment. Bile pigments were never found in the urine in quantities sufficient to give the play of colors with fuming nitric acid, and the foam test was always negative.

The daily 24-hour urinary output was at first very low in most cases, and the specific gravity was correspondingly high with the exception of Case I and Case II. In Case I, there was no urine output during the last 24 hours of life, but the anuria was not absolute as there were found 60 c.c. of urine in the bladder at autopsy. However, catheterization nine hours before death had failed to produce a specimen. In Case II, there was intense thirst, and the polydipsia kept the urinary secretion fairly high and the concentration fairly moderate. In all the other cases the forced ingestion of fluids brought the urine output fairly high and reduced the concentration.

The urine in these cases showed uniformly a high acidity. The degree of acidity was in proportion to the severity of the case and was only slightly reduced even with the marked dilution of the urine due to forced ingestion of fluids. The specific gravity varied with the urinary output; it was high at first, but became lower with the dilution of the urine. The amount of albumin present was greatest in the most severe cases and gradually decreased with the scientific management of the cases and disappeared first in the less severe cases and eventually even in the more severe cases. In the mildest cases, Case IX and Case Group X, no albuminuria was ever detected.

The urine urea, both the percentages and the quantitative outputs, and the urine chlorides, percentages and quantitative outputs, were low at first in all fairly severe cases, but under the treatment the output of these substances gradually increased in amount, and, in the milder cases, reached a fairly normal level. These figures serve as a fair index of the impaired renal functional efficiency, especially when considered with the blood urea, and an approximate average of the sodium chloride intake.

The only trace of any pathologic pigment in the urine was the reaction of the urine to dimethylaminobenzaldehyde for urobilinogen in the severe cases,

Cases II and III only. This might be interpreted as indicating a slight temporary functional impairment of the liver.

The microscopic examination of the centrifugated urine sediment substantiates the diagnosis of renal irritation that was made on the basis of the chemical and physical examination of the urine. The quantity of pathologic constituents in the sediment corresponded exactly with the severity of the cases as indicated by other findings. There were hyaline and granular casts, red and white blood cells, renal and bladder epithelial cells, amorphous urates and uric acid crystals in great numbers. At times calcium oxalate crystals, and only occasionally, the sediment of alkaline fermentation, triple phosphates, ammonium urates and calcium carbonates, were found. The sediments all improved markedly and cleared up under the physiologic therapy that was applied.

The blood ureas ranged from 10 mg. per 100 c.c. of blood in the most severe cases to 26 mg. per 100 c.c. of blood in the least severe cases. These findings together with the diminished urea output may be taken as evidence of a renal insufficiency.

The phenolsulphonephthalein excretion tests could not be made until the renal condition had practically cleared up, so far as could be determined by the chemical and microscopic examinations of the urine. The amounts excreted were high, to the extent of even suggesting a hyperpermeability. In only one case (No. III) was there any indication at all of a slow excretion of substances.

Most of the hematologic work on our cases was done between the tenth and fourteenth days after the gassing. There was noted a slight decrease in the number of erythrocytes, this decrease was most marked in the more severe cases. In Case I, the count ran as low as three and one-half million red blood cells with a hemoglobin of 70 per cent, a fairly severe secondary anemia. Even this most severe case on the tenth day after the gassing, nine hours before death, showed a persistent fairly high leucocytosis and no signs of a terminal leucopenia in spite of a definite loss of resistance against the destructive process and the secondary infection. This case showed an apparent decrease in the number of blood platelets which finding differs from that in all the succeeding cases, though the later smears in Case II toward the end also showed fewer platelets, while the earlier smears showed a marked increase in the numbers of these constituents.

Case II, as all the other succeeding cases except the last one, showed a more moderate anemia with the erythrocyte count not falling below four million and the hemoglobin totaling about 75 per cent. The leucocyte counts in Case II were seen to fall from a 29,700 leucocytosis at the tenth day to a 10,800 leucocytosis on the twenty-fifth day, the day on which he died. This was taken as an index of the gradual loss of ground or resistance in the fight. The count remained high enough even at the end, to be considered a mild leucocytosis. The blood platelets were markedly increased at first, but were not so at the end.

Case III, aside from the slight secondary anemia, showed a very gradual drop from a leucocytosis of 25,000 to one of 15,000. This drop, however, was accompanied by a gradual general improvement and a clearing up of the slough-

ing and secondary infection. There is also a definite increase in the number of blood platelets.

Case IV showed the slight secondary anemia and a marked leucocytosis of 25,000 two weeks after having been gassed.

Case V showed also the slight secondary anemia and a leucocytosis of 21,200. The blood platelets were also noted to be increased in numbers.

Case VI showed also a mild secondary anemia and a moderate leucocytosis. The blood platelets were also noticeably increased.

Case VII, the least severe of the series of generally gassed cases, showed no secondary anemia. A fairly high leucocytosis, about 20,000, was found, in spite of the absence of any marked suppuration or generalized secondary infection.

Summarizing the study of the blood in these seven cases of severe mustard gas burns we see that it shows a secondary anemia (reduction of both the number of red blood cells and the hemoglobin), a polymorphonuclear leucocytosis with disturbances in the differential count, such as an increase in the number of bone marrow elements (myelocytes, myeloblasts, bone marrow mononuclears and lymphocytes) and a definite eosinophilia. An excess of young forms of white cells is found. There is also an apparent increase in the number of blood platelets. No evidences of hemolysis were found. A very few red blood cells showing polychromasia and stippling were seen. There was no leucopenia observed in any of these cases, either during the course, or, in the two fatal cases, as an agonal phenomenon. The differential count indicates a disturbance of the bone marrow in the white cell forming group rather than in the red cell forming group. These changes can perhaps be explained by the coincident infection of the skin lesions and the respiratory tract, which all of these cases showed to a greater or less degree. The blood changes ran a fairly parallel course to the severity of the infection. The eosinophilia can be referred to the skin condition, perhaps also to the bronchial.

Under the miscellaneous laboratory examinations we must include the findings in the sputum. In general we may say that the sputum was never blood-tinged but was always more or less mucopurulent in character depending on the severity of the pulmonary affection. In Case III with a bronchopneumonia the sputum was most purulent, frothy and markedly foul in odor, and abundant in amount. On one occasion the patient expectorated a pinkish fibrin-like cast of a bronchus. Smears of this material were found to contain a mixed culture of streptococci and one of the long thick bacillary types of organisms that are found in the mouth. It seemed rational to consider these organisms as the probable etiologic factors in the secondary bronchopneumonia in this case.

The examination of the feces morphologically was negative in most cases, but in Case II at increasing intervals during the last two weeks of his life the patient passed bright red and some slightly changed blood in his involuntary stools. In his last few days the amount of blood passed gradually increased as the patient grew weaker.

Smears of the young furuncles and pus from the old furuncles always

showed a few groups of staphylococci, many degenerating polynuclear leucocytes and much debris.

The temperature charts showed febrile reactions with corresponding pulse and respiration rise, only during the presence and persistence of secondary infection. The high pulse rate in the severer cases would lead one to suspect myocardial injury. This suspicion, however, is not substantiated by the pathologic examination of the heart muscle at autopsy.

Comparing our results with the few reports of research along similar lines found in the literature, the only one of any importance on blood changes due to gassing is that of Miller (*Journal of the Royal Army Medical Corps*, January, 1918, xxx, p. 76). After an extensive amount of work he reported a new blood change in gas poisoning as follows:

1. In cases of gas poisoning in which symptoms persist, there is an increase in the number of lymphocytes relative and absolute in the circulating blood. In slight cases this may not be beyond the normal limits or in excess of what may be met with from other causes. In any marked case, however, the changes are sufficiently striking to be of some importance in cases where the medical officer is in doubt as to the reliance to be placed upon the statements of men complaining of having been gassed.

2. The blood change is elicited by a differential count of the leucocytes, and it may be taken that a count in which the percentage of lymphocytes approaches that of the polymorphonuclear leucocytes indicates that the patient is still suffering from the effects of the gassing, i. e., provided there is no other complicating disease present which might produce a similar change. A slight relative lymphocytosis is not an uncommon finding in men from overseas, or in anyone, so that no great reliance can be placed upon the signs unless the percentage of lymphocytes approaches closely that of the polymorphonuclear cells.

3. The cell which is increased is the ordinary small lymphocyte of the blood. There may be in some cases a diminution in the number of polymorphonuclear leucocytes which will of course accentuate the sign, but the increase of lymphocytes is an absolute one. Morever, it appears in cases with a high leucocyte count.

4. The change is one which develops early, probably within a month of the gassing and continues for a long time; in cases with persistent symptoms for at least eighteen months.

5. The change appears to be independent of the kind of gas and it is shown by patients exhibiting many varieties of symptoms.

Our findings are not in accord with the above conclusions for all gases, and our cases may not be comparable with his. It seems to us to be questionable whether Miller studied and included the blood findings in cases of mustard gas poisoning. He mentions only the two groups of drift gases and shell gases, and does not differentiate the subclasses chemically at all. His last article published early this year came late enough to have the blood changes produced by mustard gas included, yet no mention is made of it and on the basis of the symptoms described we can not conclude that dichlorethylsulphide cases were studied in this series. We discuss this paper because Miller claims that his

sign is present in all chronic gassed cases regardless of the kind of gas to which they had been exposed and independent of the symptomatology presented. Then, too, the pathologic conditions which he favors as the most probable etiologic factor in the production of the lymphocytosis, that is the chronic inflammatory change in the respiratory tract and in the gastric mucosa could very well be present in chronic mustard gas cases. We do not think that such conclusions can be drawn for all types of gassing as yet, but the decision must rest with the results obtained from further studies of cases in which the chemical nature of the gas is known.

Moreover, our findings do not agree at all with those of Pissarello; but it is possible that his negative findings in the urine were due to the mild character of his cases, corresponding to those in our Case Group X.

Mandel and Gibson's observation on the frequency of albuminuria in cases of mustard gas poisoning is confirmed by our work.

CONCLUSIONS

1. Mild cases of mustard gas burns of the skin show no changes in the blood or urine.

2. Moderately severe and severe cases of mustard gas burns of the skin with some involvement of the upper respiratory tract show after the first week definite changes in urine, blood urea and blood.

3. The urinary changes consist in a diminution of the urinary output, increased concentration and acidity, albuminuria, and diminished urea and chloride output. In the sediment there may be found casts, renal epithelium, red blood cells and an increased number of leucocytes. Under forced fluids prompt improvement occurs.

4. Coincident with these urinary changes the blood urea is found to be high, but approaches normal with the improvement in the urinary condition when fluids are forced.

5. The blood shows a slight secondary anemia with a well-marked polymorphonuclear leucocytosis, a definite eosinophilia, and the appearance of myelocytes and young forms of leucocytes. The blood platelets were usually increased. No evidence of hemolysis was found. These changes indicate a disturbance in the white cell formation rather than in the red blood cell group. No leucopenia was noted at any time. The leucocytosis reached its height coincidently with the height of the secondary infection and fell with the improvement of the infection.

6. The temperature, pulse and respiration charts show in the severe cases an initial period of shock. With the development of the necrosis and the secondary infection there is a corresponding febrile reaction.

7. The bacteriologic examination of the infected skin lesions and furuncles showed constantly the presence of staphylococcus pyogenes aureus. In the one bronchial cast obtained streptococci were present.

8. We believe that the changes in the blood and urine may be interpreted as dependent upon the secondary infection and, in part, possibly, to the absorption of toxic products from the necrotic skin, rather than to any direct toxic action of mustard gas.

My thanks are due to Doctor A. S. Warthin for directing this work, to Captain L. L. Roos for the privilege of studying the cases under his care and to Doctor C. V. Weller for many helpful suggestions.

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DIAGNOSIS PER EXCLUSIONEM IN ORDINE: GENERAL AND PSYCHIATRIC REMARKS*

By E. E. Southard, M.D., Boston, Mass.

IS there any excuse for a communication on the general theory of clinical diagnosis? Should not one in the present concrete state of medicine apologize for any generalization or theoretical handling of a topic which has long since passed into the realm of the dead? If medical schools rarely nowadays, and only as a *curiosum*, deal with the sometime familiar disciplines of so-called medical propedeutics and the logic of medicine, is it not for the very good reason that medicine no longer requires any propedeutics or any special overhauling of its logic?

I have two possibly tenuous excuses for the attempted resurrection, namely, first, that it is a canon of mental hygiene to get in imagination as far away as possible from our terrible environment; and secondly, that the realm of dead notions somewhat well befits a pathologist who has gone into psychiatry.

Speaking to a group of eminent clinicians, I need not insist that I myself make no claims to being a diagnostician of the first water. But just as more or less valuable books on elocution are written by persons without color or pretence of oratory, so perhaps one who is not an especially good diagnostician may descant humbly on the matter. Some five years ago, when I became director of the newly founded Psychopathic Hospital in Boston, it became for the first time my duty to deal concretely with a large series of clinical diagnoses. To be sure, before that time, and in fact, in the year 1909, I had been charged with the task of supervising the clinical and pathologic research work of the state institutions for the insane of Massachusetts, and had already at that time begun to agitate upon the manifest errors in diagnosis which appeared in a small but definite minority of cases of mental disease in these institutions, as tested by the stern criteria of the autopsy table. I took an especial interest in errors of diagnosis in that mental disease entity, about which we know the most, namely, general paresis,[1] and found that one of the most active and thoroughly educated state hospital staffs in the country, namely, that of the Danvers State Hospital,[2] was none the less able to make an error of anywhere from 5 to 15 per cent, according to the fineness of the criteria adopted in the disease general paresis. After all, this work and sundry other articles by my associates and myself[3,4,5,6] remained quite upon the theoretical or unapplied level.

Suddenly, in 1912, I was translated to a region in which exceedingly rapid, not to say provisional, or not to say "snap" diagnoses had to be rendered in what almost any one would concede was the most difficult field of clinical diagnosis, namely, the diagnosis of mental disease. When it is remembered that the task at the Psychopathic Hospital is largely the temporary care of acute, incipient, and curable cases together with a consideration of all the most du-

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bious cases in the community,[7] it will be seen that the problem of a reasonably accurate diagnosis in these cases is not at all easy. It is necessary to remember, also, that our task is not that of the alienist so much as that of the psychiatrist, employing these terms in the differential sense recently advocated in a paper on the nomenclature of mental hygiene.[8] It is not the task of the Psychopathic Hospital to determine, except in a minority of cases, the committability or survivability of its patients. Of the first 5000 discharges from the Psychopathic Hospital, over 1700 were discharged as "not insane," a term which signifies, not that the patients had recovered, but that they were regarded as not having been insane during their stay at the hospital (the recoveries are over and above the 1700 "not insane"). In short, the task here is one of securing a basis for treatment and counsel for cases that lie often entirely without the purview of governmental control as mechanized by the probate courts. A large part of our problem is medical in the strict sense and not medicolegal.

I may be pardoned for insisting upon this peculiar and almost unique feature of the Psychopathic Hospital work in Boston, because not even my colleagues in the specialty of mental diseases have readily grasped the point. *Alienists* are a type of physician specializing in medicolegal practice, and their task is to determine alienation; that is, the theoretical or practical committability of their cases in the interest of the public welfare. *Psychiatrists* are a type of physician specializing in mental diseases on a much broader basis, namely, the basis of finer diagnoses, involving groups of mental disease and defect, and the psychopathic trends which fall short of defined psychoses and even the quicksand topics of eccentricity, crankiness, and oddity. *Alienistics*,—a medicolegal field,—is pretty sharply distinguished from practical psychiatry,—a medical field. A good psychiatrist ought to be able to accommodate himself to governmental groups well enough to be a good alienist; but, on the other hand, many a good alienist who has dealt for years with the category of committability only, is unable quite to see the point of a diagnosis of "Psychotic, not insane," or of "Psychopathic, not insane." The question of nomenclature is subordinate; but aside from the question of nomenclature, if the practitioner can not grasp the distinction between insanity in the medicolegal sense and mental disease in the medical sense, he is a man unable to keep pace with the modern progress in psychiatry.

What, we may ask, has the question of psychopathic hospital diagnosis of psychoses that fall short of insanity to do with the topic assigned for this communication? How does this work fit into a discussion of the general theory of clinical diagnosis? Psychiatrists have always taken a good deal of interest in classification. I will remind you only of the eminent instance of Pinel, who in 1809, published a *nosographia methodica*, which is one of the best-known of the old nosologies, a very good general view of which is given in Hosack's publication in 1819.[9] I am afraid, however, that most modern practitioners, and especially in America, would be apt to deride it as out of date, if not fundamentally beside the point of these adventures in classification. Of course these scoffers have the entire interest of science against them in their scoffing. But the modern practical fellow, especially the pragmatic American, little recks such a

small matter as consistency with the general history of science. Nor will I attempt to defend the various excesses of nomenclature to which my psychiatric superiors, both in point of time and in point of capacity, have sometimes perpetrated. It is another queer way which Americans (and I suspect other moderns) have, namely, to confuse the topic of nomenclature with the topic of classification. Classifying for these persons means assigning a name. To be sure, a slight re-reading of that apostle of clarity, John Stuart Mill, would perhaps set these confused minds aright. Still I suppose it is too much to ask of them to re-read even a few chapters of Mill's *System of Logic*.

What, after all, constitutes diagnosis? I do not know whether the Harvard Medical School curriculum is less logical than those of other medical schools that the American Medical Association terms *Class A*, but it is very hard to get from a Harvard Medical School student at any stage, even immediately after securing his M.D., an adequate definition of the terms *diagnosis*, *symptom*, and the like. Yet would any one of us suppose that these terms can be safely dispensed with in practice or in theory? And even if you could somehow show that a pragmatic view of medicine might throw overboard altogether the distinction between disease entity and disease symptom, nevertheless the books are full of these terms used in a variety of ways, and I am sure it ought to be the duty of every medical course to offer some pabulum (whether propedeutic or by way of appendix) on these matters, which were doubtless comprised in the forgotten and discounted field of so-called Medical Logic.

Many a favorite textbook in the practice of medicine fails to make any point whatever of this distinction, and plumps one forthwith into a discussion,—e. g., of typhoid fever,—jauntily assuming that the student somehow knows by intuition the meanings of the terms, *definition*, *entity*, *diagnosis*, *symptom*, *symptom-complex*, *syndrome*, and the like. Perhaps, however, it is better to leave out general remarks in this direction than to put in some which are found in certain other textbooks that have run into many editions. Strümpell[10] makes no special point of the matter but insists in a preliminary note upon the importance of diagnosis, of clinical observation, and of keeping the common courses of all diseases in mind. Here, perhaps, is the most commonplace remark nowadays about diagnosis: diagnosis, namely, is constituted by observation, according to these authors. In fact, there is one textbook (Wilson[11]) that summarily states upon its title page, that the whole art of medicine is in observation. On a later page, it is insisted not quite so broadly, that "It is certainly true that the art of diagnosis is an art of observation;" and again, "The facts of pathology and semiology and the natural history of the diseases constitute the basis of diagnosis." This latter statement seems almost equivalent to the statement that the facts of disease are the basis of diagnosis, which may be in one sense true, but is so little helpful that it might well be left unsaid. Another recent author (Hall[12]) states that "The art of diagnosis consists, then, in gathering all accessible data and arriving at that conclusion which seems the most reasonable as the probable cause of the trouble." This definition evidently goes beyond the former, namely, "Diagnosis is constituted by observation," by considering that the reason is necessary over and above observation. Put in these terms, of course no one of us would care to say that diagnosis consists in gathering

data. Put baldly, it is certainly untrue to say that the collecting of facts constitutes the art of distinguishing amongst these facts. Yet the whole trend of recent work runs in the direction of insisting upon observation at the expense of reason. And, whether or no we teachers are entirely clear in our own minds as to the distinction between diagnosis and the mere recognition of fact as such, certainly our students are not always clear. A student will give the "diagnosis" *fever* or *rose spot,* when he would scoff at making the "diagnosis," *It is raining,* or *The engine is skipping.* If this be diagnosis, make the most of it! Of course, diagnosis is clearly a form of recognition, a form of knowledge, but there seems to be no warrant in raising every elementary form of awareness, kenning, or recognition to the level of diagnosis, which term bears within itself a manifest prefix, suggesting distinction, differentiation, sundering. All my own medical teachers, and I do not doubt the majority of those of my listeners, insisted upon the value of accurate observation. Few of them insisted upon the importance of correct reasoning. Most of them, I take it, partly as a matter of self-defense as they were growing older, were quite sure that maturity of judgment was a thing not readily attained. It never seemed to occur to these teachers that, as the powers of observation were on the wane, the powers of right judgment were to increase. In brief, these teachers, without ever once using the term *logic,* and hardly ever the term *reason,* managed to get into their homilies for students the idea that there was something besides observation, namely, what they called common sense or knowledge of fundamentals, or keeping essential cases in mind, or ripeness of clinical experience, and the like.

Though I believe some course in propedeutics might well be constructed to contain the main principles of the logic of medicine, yet that is not the point of the present argument. Basing my notion upon the practical experience of the last few years, in which I have had contact with clinical diagnosis, always with the autopsy criterion more or less consciously in mind, I want to argue for a more extensive application of the principle of logic in practical diagnosis, and especially the practical diagnosis of the tyro. Perhaps you will think my argument is nothing more or less than a rehabilitation of the diagnosis by exclusion of the older authors. To some extent, the argument does follow that line, though the arguments have been derived from recent practical experience in off-hand and professional diagnosis, and from certain logical considerations. That older argument is found very well expressed in DaCosta's book so long ago as 1864.[13] DaCosta's book, according to an enthusiastic Philadelphian (Wilson[11]) marked an epoch in the progress of internal medicine; and surely many of DaCosta's distinctions are found in several textbooks built upon the lines of his book for many decades after 1864. DaCosta distinguished direct and indirect diagnosis. Indirect diagnosis by exclusion, according to DaCosta "is not on ordinary occasions much employed *nor indeed is it to be recommended*" (italics mine). It is this dictum of DaCosta which I would think ought to be combated in any summing up of present-day processes in diagnosis.

The reasons why DaCosta felt that diagnosis by exclusion was not to be recommended were assigned by him as follows: First, "to prove what a thing is by proving all that it is not, is a very tedious process." Secondly, DaCosta went on to say, "it is difficult to think of all the possibilities." And thirdly, he

said, "pathology is in an imperfect state." Now, as for the latter two reasons, it is clear that the process of direct diagnosis is equally subject to the pitfalls of imperfect pathology, and equally subject to the charge that it is hard to think of all the possibilities. I myself can only believe that these two latter so-called drawbacks are not drawbacks worse for diagnosis by exclusion than for any other form of diagnosis. Accordingly, I believe that DaCosta's objection to diagnosis by exclusion reduces its tediousness; but should we hesitate to say to our students that it is better to be tedious than wrong? The technic of DaCosta's process may be elicited in his own words:

"To cite a case in illustration. A person consults us for a cough brought on by exposure. He has been sick for four or five days, having been previously in good health. We notice, on examining him, that his breathing is hurried, and that he has fever; the lower portion of one side of the chest is dull on percussion, and the respiration there is wanting; the action and sounds of the heart are normal. The facts point to the lung or its covering as the seat of the disorder. We know, furthermore, from the history and the febrile symptoms, that we have to deal with an acute affection. What are the acute pulmonary affections? Acute bronchitis; acute phthisis; acute pleurisy; acute pneumonia. In all there is fever, cough, and impaired breathing. Is it acute pneumonia? No; for, notwithstanding there is in this complaint, in addition to the general symptoms mentioned, dullness on percussion, such as we have here, the dullness is associated with a blowing respiration; whereas in the case before us no respiration is heard. Let us look at the sputum, and see if it is tenacious and rusty colored. It is not; it is thin and frothy. Moreover, the breathing, although hurried, is, when counted, found to be less hurried than it is in inflammation of the lungs. But acute pleurisy may explain all the signs. The patient, too, when questioned, states that he had at the onset a sharp pain in his side; and this we are aware takes place in pleurisy. The vocal vibrations, likewise, are noticed to be absent on one side of the chest, which, when carefully measured, is evidently enlarged. This corresponds in all points with what happens in pleurisy in the stage of effusion. The disease *is*, therefore, acute pleurisy in the stage of effusion. We finish the diagnosis by ascertaining the existence or nonexistence of other maladies, and by taking note of the severity of the complaint; that it has occurred in a young and robust person of good habits; and that the symptomatic fever is very active."

But what is a direct diagnosis,—one not made by exclusion? According to Wilson, "A direct diagnosis is made when the history of the case and the clinical phenomena are sufficient to warrant a positive conclusion." Wilson goes on to say that a diagnosis by exclusion differs from differential diagnosis only in scope. Strange as this phrase may sound, it strikes me that there is a good deal of truth concealed in it. I feel that, so far from admitting with DaCosta, that diagnosis by exclusion is not much employed or to be recommended, practically every diagnosis is by exclusion, whether consciously or unconsciously.

Musser remarks concerning diagnosis that "the data collected are sufficient to warrant a positive conclusion. The direct method is scientific, rational, and most practical. It is a practice of purely inductive reasoning." I am not sure whether it would not be sounder to say that it is a process of purely *deductive* reasoning, but modern logicians have conclusively enough proved that practically all reasoning is both inductive and deductive, so that it would not pay to quibble over the claim that direct diagnosis is "a process of purely inductive reasoning." As to the method of diagnosis by exclusion, Musser remarks, "Thus, a symptom group may suggest several diseases; each affection must be passed in review and excluded until one is found which closely corresponds to the data of the case under consideration." In short, it would seem that diagnosis by

exclusion is an effect of the *force majeure* of complex and obscure data. The battle is easily won when it is a question of perceiving a symptom and suspecting a disease, whereupon all "the data collected are sufficient to warrant a positive conclusion."

Now, possibly it is the complex and obscure nature of mental disease which has caused me to feel that diagnosis by exclusion is a method that requires rehabilitation in the minds of teachers and in the pages of textbooks. In medicine and biology at large in the middle of the nineteenth century, it was the fashion to denounce speculation and extol observation. So many of the medical and biological sciences depended upon the microscope and the visual process, that nothing was more natural than to see great virtue in observation as compared with the vagaries of the *Naturphilosophic*.[15] We are now so far beyond the range of that old *Naturphilosophie* (unless the idea of Pan-Germanism may be regarded as a remote result thereof), that it should be quite safe to uphold the reason as entitled to a seat beside observation in the process of diagnosis. Applied logic accords to observation its full worth. Secondly, a proper value is assigned to what may be inaccurately summed up in the phrase *comparative method*. It is the comparative method probably that is being used in diagnosis for the most part at the present day. That is, one picks a symptom, suspects a disease, constructs a supposititious diagnosis, and proceeds to compare it with all the data of memory or reference books. It is all one, whether you pick one symptom—e. g., the so-called presenting symptom[15] popularized by Richard Cabot,—or assemble a symptom group; the process remains the same, that of matching the data of the case with some supposititious diagnosis. Now in the field of mental disease probably every one of you has had the experience of matching virtually all the symptoms of a case with the majority of those given in the textbooks for several different mental diseases. In short, the comparative or matching process has been only too successful, and the diagnosis might well be rendered by lot from amongst a not very small group of textbook headings.

Of course, the comparative method involves the use of observation also. The distinction between observational recognition of a condition and the comparative determination of a disease by a direct method, is not a mutually exclusive distinction. So also in respect to the third method of applied logic, namely, the statistical method. The statistical method requires both observation and comparison, but entails also certain new features. Probably Richard Cabot has popularized the statistical method of diagnosis more than any other recent author. Cabot finds a presenting symptom which becomes to him a lead. This presenting symptom is often something complained of by the patient, but also is often something noted by the physician that the patient did not subjectively recognize. Cabot has founded a differential diagnosis upon a selection of the most common presenting symptoms. He goes on to list the causes of these symptoms by their frequency, and then, to use his picturesque phrase, "follows the symptom home." Following the symptom home means, naturally, employing all manner of comparative and observational methods in addition to the merely statistical one. Nor do I wish to give the impression that Cabot overemphasizes the statistical method in his account. He merely emphasizes it more than most previous authors. Nor would his account fail to insist that observation is indis-

pensable, for he carefully states that diagnoses are missed usually because physical signs are not recognized. That is, for Cabot, poor diagnosis is usually a matter of poor observation. But occasionally diagnoses are poor on account of poor reasoning, and Cabot's book is an argument for a more comprehensive grasp of the possibilities of diagnosis. Others may insist upon the recognition of the symptoms and signs by proper methods of observation, and Cabot, like many others, has in other works given an account of these matters along approved lines; but he dreams for the purpose of differential diagnosis of a "cash-register of causes." He wants possibilities sifted. He wants clues, radiations, and leadings followed out along lines that are essentially statistical. One proceeds from the presenting symptom to the possible causes; from the possible causes to the probable causes, and from the probable causes to the actual cause. In the technic of this determination, Cabot, as is well known, much insists upon the statistical configuration of the different conditions in which the various presenting symptoms are found.

Cabot notes that physicians in the matter of differential diagnosis "are very suspicious of any attempt to tabulate their methods of reasoning." He speaks of profiting much by Herbert French's *Index of Diagnosis*[16] (first published in 1912), a book which I find is greatly affected by medical students of my own acquaintance. French claims his index to be an index of main symptoms, though there seems to be no internal evidence in the book just how these main symptoms were selected. French, like Cabot, deals largely though not exclusively with symptoms complained of.

It is readily seen that Cabot's ideas (though they would have been readily comprehended by DaCosta in 1864, since they are founded upon the statistical principle which had already been a few decades in vogue in DaCosta's time) would not have appealed especially to him as important in the process of direct diagnosis. Feeling as DaCosta did concerning diagnosis by exclusion as a *dernier ressort*, he would not have seen the compelling value of Cabot's statistical frequency tables for the distribution of symptoms in different conditions. Moreover, it is doubtful whether in 1864 hospital records were so extensively kept as nowadays, despite the fact that intensive records of special cases may have been kept at a relatively higher standard than now prevails in institutions where the real work is done more by interns than by visiting physicians.

The situation, then, is that in some cases what might be called an observational diagnosis can be rendered. Personally, I should feel that the term *diagnosis* was being prostituted somewhat when the diseased condition is recognized forthwith on the basis of some pathognomonic symptom or combination of symptoms. But let the phrase pass; the result of naming the disease and getting a practical basis for treatment is attained by a process of pure observation. The so-called direct method of diagnosis is hardly on a higher plane logically speaking than that of observation in many cases; but in others, and perhaps in the majority of cases, this process of differential diagnosis by the so-called direct method, is one of comparison; that is, of matching the phenomena of the disease observed with those of some classical or textbook type. The unduly maligned method of indirect diagnosis, or diagnosis by exclusion, likewise employs comparison inasmuch as it excludes disease after disease by discovering that not

enough exists to match the types in question. Having risen, accordingly, from a process of direct recognition (*gnosis* rather than *diagnosis* in any logical sense) to a process of somewhat less direct differential diagnosis by a positive matching or a negative excluding process, we finally arrive at a more modern technic of studying the frequency of symptoms in certain large groups of comparatively well observed cases (the majority of Cabot's tables deal with 250 cases analysed at the Massachusetts General Hospital). We notice that the process of observation is indispensable throughout. Extreme exactitude of observation is not perhaps so necessary in statistics as in individual cases; at least errors of observation may be assumed to balance themselves to some degree.

Is there no further sharpening of our technic of diagnosis? In the practical handling of the diagnostic problem at the Psychopathic Hospital, in the course of two years' observation I became interested in the fact that, where diagnoses were not matters of mere observation and direct differentiation, but where processes of exclusion were necessary, I found myself endeavoring to exclude conditions in a certain *definite order*. It is this ordinal principle which I believe might constitute an advance in practical diagnosis, were it to be insisted upon in still other branches of medicine than psychiatry. I have recently made some endeavor to apply the principle to the situation in clinical neurology but shall not here mention the results of that inquiry in any detail. After the first two years of off-hand and provisional diagnoses at the Psychopathic Hospital, I then considered the matter of exclusion in a definite order for some three years before laying down the order in question (see below). I think it would be presumptuous for any one in any special branch of medicine to draw up a definite order of diagnoses in any other. For example, however convinced I might be that diagnoses in dermatology are actually made consciously or unconsciously by some process of successive exclusion of conditions in a definite order, I should not (as I am far from being a dermatologist) have the slightest ground for suggesting an order for dermatological diagnoses, or a list of conditions to be put in order. Not being an internist in the field of cardiac disease (that is to say, not being in any sense an expert with the electrocardiograph and all the rest), I certainly could not advocate any particular order of diagnosis for heart disease, however strongly I might be convinced that such an order must exist.

At this point, I looked into certain works on logic to learn what might be said concerning these different principles of diagnosis, and found in the late Josiah Royce's contribution entitled "The Principle of Order" in the *Encyclopedia on Philosophical Sciences*, an exposition very much to the point.[17]

I presume that most of us have few memories of logic except the syllogistic logic of such college textbooks as that of Jevons. Some of the older amongst us will still have used Mill's *System of Logic*, or textbooks closely modeled thereupon. The more recent advances in applied logic are a closed book to most college and medical students, but in addition to so-called formal logic used as an irregular discipline in most colleges, there is an applied logic or methodology which deals with the norms of thought as applied to the methods of the special sciences. The formal logic of a book like that of Jevons is only a very subordinate part of logic as at present defined. Royce speaks of the new doctrine as

the science of order. This science, he says, is today in a very progressive condition, is in some notable respects new, and offers inexhaustible opportunities for future progress. Already in the Socratic and Platonic handling of these topics, the systematic nature of the world's construction, the objectivity of the world permitting inference concerning its various truths and the order that rational processes show, had already become clear. Types, forms, and relations are at least as real as the facts of the physical world. Aristotle, Bacon, and still more importantly, Galileo, made important advances in logic. Today no one will question that every science in dealing with its facts must employ methods of classification, in no wise different from the method used by Socrates in his dialects. To be sure, a science which uses only methods of classification must now be regarded as a very young science. Botany and zoology have long since passed the phase in which classification is the dominant interest. Anthropology, on the other hand, is largely classifying still, though there is some tendency to the development of a higher method of logic, the comparative study of the forms and results of human culture.

Royce mentions that, amongst the medical sciences, psychiatry is just now emerging from a stage in which the bulk of the science was made up of the classification of cases, symptoms, and disorders. Psychiatry is now about to work on a higher plane of methods. The more complex the facts, the harder it is for a science to get beyond this first stage of classification.

What are these higher processes of applied logic? There are mainly two: The method of comparison, and the statistical method. The comparative method compares the corresponding stages in the various processes of products of natural evolution in the science in question; whereas the statistical method uses exact enumerations as the basis of its science. Of course, the two methods are not always sharply to be distinguished; whenever one has to compare numerous evolutionary processes, all the results of these processes have to be enumerated. In these instances, however, the statistical method is merely an auxiliary to the comparative method. When, however, we come to such matters as the mortality tables of insurance, the sociology of marriage and divorce, of suicide and crime, or of commerce and industry, we are dealing with topics in which the statistical method is virtually the only one at present available. We study, for instance, how human mortality varies with age; how the science of an organ or an organism follows conditions determined by heredity or environment. As a result of such statistical processes, the statistician becomes able to deal with aggregations or blocks of facts; orders or aggregations which may be treated as units of a higher order.

When sciences become developed still further, these two methods of comparison and statistics are used in a still more intimate manner, combined in a method which Royce terms the *organized combination of theory and experience.* By means of the statistical and comparative method, we discover laws of nature that have a certain degree of probability, the degrees of which we may trust on the basis of fair samples of the phenomena of the given science. We then construct laws on the basis of hypotheses derived directly from fair samples of fact. Hypotheses thus drawn may be of the simple type directly

refutable or directly verifiable by immediate recourse to the facts; or on the other hand, hypotheses may require much more work for their testing. In fact, the more direct the proof, the more valuable the hypothesis, since the success of the hypothesis would here depend upon the falling-in-line of vast numbers of facts which on no other basis could be supposed to fall in line. To combine hypothesis, theory, and observation, we first draw up a hypothesis regarding the constitution or laws of some region of physical fact. Upon the basis of this hypothesis, we make an extensive and exact deductive theory as to what *ought* to be present if the hypothesis is true. "The more extensive, exact, and systematic the theory thus made possible proves to be, the larger are the possible samples of the consequences of the hypothesis which are available." We then collect samples of facts by means of observation and experiment, and proceed to compare them with results of our elaborate deductive theory. The more elaborate and extensive our theory, the larger the range of facts that we can draw upon for comparison. We are not now restricted to noting what proportion of members of a sample have certain characters. On the other hand, if the deductive theory is a highly developed and elaborate one, we shall find that almost any sample available for comparison is minutely verifiable in detail with some part of the original hypothesis. In short, the value of this method depends upon "the exactness, the order, and the systematic character of the concepts in terms of which the hypotheses thus directly tested are defined." It would thus appear from this highly condensed statement of Royce's view, that "the organized union of theory with observation requires for its perfection concepts and systems of concepts which permit of precise and extended deductive reasonings." It is surprising how small the samples need to be when it comes to a judgment as to the applicability of a highly complex hypothesis. A few small samples taken from widely separated parts of the system will prove or disprove the virtues of the hypothesis.

Without asserting that medicine is yet in a stage to profit like physics and chemistry from this organized combination of hypothesis, theory, and observation, it is clear that many parts of medicine are far beyond the application of mere statistics or of mere comparison, and still farther beyond the modest virtues of pure observation.

Without venturing further at this time into methodology and modern applied logic, it is clear that mere observation, mere comparison of stages, mere enumeration, are not the whole story in any science. If the medical sciences are going to advance in their logic, it is more than likely that their logical advance will take place in the direction of a greater insistence upon order. I hold accordingly that, if Royce's exposition of certain modern developments in logic is a sound one, the next stage of development in medical thinking will be a reduction of its interests more and more to order and system. There is reason to hope that by the reduction of medical as well as any other scientific facts to order systems, a greater and greater success in deduction will be attained. I conclude, therefore, that when I found our process of diagnosis at the Psychopathic Hospital employing more and more the concept of order, I was simply discovering a small fact bobbing in the big stream of logical advance.

In the light of present knowledge, how almost naïve and childish appears the old dictum that disease is life under altered conditions! Here were but two elements: life on the one hand, and change on the other. Each contains a host of undiscovered statements of fact. How slender a contribution appears the claim that diseases must be instances of either the augmentation, the diminution, or the mere modification without increase or decrease of structures or functions. To be sure, bacteriology shortly yielded a dyadic system of germ on the one hand and host on the other, which for the moment and for a decade or so allowed one to hope that the formula "Disease is life under altered conditions" might be simply rendered into, "Disease is the effect upon an organism of a germ." Then came the contentions of Metchnikoff concerning phagocytosis, and the more complex interrelations of the host with its contained germ.

Shortly, in the nineties arrived triadic conceptions of the interrelation of the organism, the foreign substance, and sundry intermediary bodies; and early in this century was unfolded the still more mysterious situation of anaphylaxis. In short, the problems of medicine are becoming more and more rich and complex, more and more verifiable by small samples of fact taken at widely diverse parts of the system.

The rapid complication of the research situation in medicine at large, as typified especially by the facts of immunology, has its reflection also in the slower moving departments of clinical diagnosis. We see in textbook after textbook insistence on diagnosis as a matter of observation (going back very far, for example, to Baglivi[18]). We then found, as in virtually all the medical textbooks in the latter half of the nineteenth century, a new form of assurance: The diagnostician is not now satisfied with what he calls direct diagnosis.

The aim here is to enroll the case in some definite group of diseases recognized by pathology. The difference between perceiving that "this fruit is an orange" and scientific recognition of a diagnosis is merely a question of degree. It is not so easy to say that "this is a case of typhoid fever," as it is to say that this fruit is an orange, because of the more concealed and special nature of the points on which we rest our diagnosis of typhoid fever. The method is one of comparison of certain perceived characters or features with certain signs already known to us as pertaining to certain disease groups. Whether the symptoms are simple, like a friction rub, or complex, like the chemical analysis of a secretion; whether the symptoms are present at the time of examination or are merely anamnestic, from the diagnostic point of view, they are speedily divided into pathognomonic symptoms on the one hand, and more general ones on the other. The tubercle bacillus or the Argyll-Robertson pupil might be mentioned as examples of pathognomonic symptoms in this broad sense; whereas fever and vomiting would be examples of symptoms which belong in a great number of disease groups. But whatever the kinds of symptoms we recognize, the process of diagnosis appears to be one of comparison of those symptoms that we perceive with such symptoms as we know to characterize a given group of diseases, and upon the discovery that the symptoms of the disease in hand correspond with the symptoms of the disease type

which we know from the books or from experience. We draw a conclusion, then, on the basis of similarity of symptoms. We may draw this conclusion from a pathognomonic symptom, which beyond any question indicates the existence of a given disease; or if no pathognomonic symptoms are present, we may ground our diagnosis upon the harmony between the general symptoms in our patient and the symptoms that belong to some described disease; and of course we are throughout well aware how unsuccessful may be a diagnosis based largely on the similarity of general symptoms to those of the books. This method of diagnosis, which we may briefly term the "type-matching" method, is doubtless the one extolled by the older workers under the name direct diagnosis. It represents an advance upon purely observational diagnosis,—that is, diagnosis by inspection,—and is a form of diagnosis by comparison.

Diagnosis by exclusion or by differentiation is a method somewhat decried by older workers and now brought into great prominence by such work as that of Cabot and of Herbert French. Though there is nothing logically new in this work, there is a new emphasis in it. It is still, logically speaking, an application of the comparative method greatly bolstered, as Cabot handles it, by the statistical method.

The general nature of differential diagnosis is somewhat as follows: As it is imposible to consider all the phenomena in a given disease, we first select a group of diseases in which a certain sign is found. We look in the case under observation for some more or less outstanding symptom. This common symptom which we would use as the point of comparison amongst diseases, is called by Bieganski the *index of differentiation* or the difference indicator. Cabot has more recently termed one form of it the presenting symptom. This indicator or presenting symptom is chosen because we by experience know that it occurs in a large number of diseases. To be sure, it is much better not to take a too-general indicator. Thus, in the question of typhoid fever, it would not be so advantageous to begin with fever, perhaps, as to begin with diarrhea. The process of differentiation now begins: We compare the case under observation with those diseases which we have found to be somewhat similar thereto. We pass from one disease group to another. We constantly keep upon one side the observed case with all its symptoms, and on the other the total series of diseases which in a certain respect are similar to it, namely, in respect of the common trait, index of differentiation, or presenting symptom. We proceed to look for differences. The observed case may not belong in a group because it does not possess the symptom which is constant in that group; though the indicator is possessed by both diseases, a symptom constantly present in the compared type is absent in the observed case.

Or the observed case may not belong in the compared group because there is a symptom in the observed case which never occurs in the compared group.

Again, the observed case is not the disease with which we are comparing it because we know that in the compared disease a symptom constantly occurs which is the direct opposite of some symptom observed in the case in hand.

Moreover, there may be an incongruence of symptoms of a quantitative or qualitative nature, a difference which does not proceed to the point of complete absence or perfect antagonism of symptoms.

Following is a table which embodies the process-types of clinical diagnosis now in vogue:

TABLE OF PROCESS TYPES OF DIAGNOSIS

I. Inspection.
II. Expectation.
III. Induction.
IV. Comparison
  (a) Similarity.
  (b) Similarity and difference.
  (c) Difference.
V. Ex juvantibus.
VI. Ex nocentibus.

I may say at the outset that it is the endeavor of this paper, granting each of the three subordinate methods under the head of Comparison to be a separate logical method of diagnosis, to add a ninth method. This ninth method I shall choose to call "*Diagnosis per Exclusionem in Ordine.*" *Diagnosis per exclusionem in ordine* is merely a method of employing logical comparison of Type IV (c) of the above table *in an orderly manner.*

But before attempting to speak of this newly described type of diagnosis I must briefly describe the eight classical methods so that I may, if possible, demonstrate that the ninth or proposed new method has novelty. For the purposes of this discussion I have gone rapidly over a great many of the older textbooks of medicine, studying largely the logical remarks by their authors in the prefaces and introductions thereto. I then examined many of the textbooks in Medical Logic which were for some years the vogue in medical schools. From the study of textbooks, largely in the latter half of the nineteenth century, and from the study of works on Medical Logic I have arranged and combined the methods of the above table. I have been especially aided by the modern work of Bieganski, a Polish work available to me in German translation from its second edition. This work may be referred to for a good summary of the older points of view, together with the fruits of some Polish polemic in which Bieganski had for some years been engaged. The older work of Oesterlen,[20] published in Tübingen in 1852 and translated into English[21] in the Sydenham Series in 1855, is almost barren for modern purposes (so much so that I found the leaves uncut both of the original and of the translation in the New York Academy of Medicine!) Of still older literature, the Medical Logic of Sir Gilbert Blane,[22] illustrated by conclusions concerning yellow fever, is of great interest, though his classification of the elementary principles of life as generative, conservative, temperative, assimilative, formative, restorative, motive, sensitive, appetitive and sympathetic, is an example of categories which, however true and from various points of view feasible they may be, are of little diagnostic value. This older work often fails to distinguish the question of classification from the question of what is to be classified. Sir Gilbert Blane's work upon yellow fever, and especially upon scurvy, derived

from his expert contact with marine diseases in the British West Indian campaigns, is of greater value than his excursions into logic. Blumenbach calls Sir Gilbert Blane the most learned and classical physician of the age, but despite this German appreciation, little has been done in Germany of an original nature on medical logic. Oesterlen appears to be in the general nature of a physician's reaction to the logic of John Stuart Mill. Apparently someone was impressed with the possible value of such work as Oesterlen's, and Francis Ogston was given a new chair in Aberdeen as Professor of Medical Logic and Jurisprudence. In a syllabus[23] of his highly interesting course of thirty-two lectures, he refers to his indebtedness to John Stuart Mill and to Oesterlen, traces the history of the topic from Aristotle to Bacon, thence to Blane and Oesterlen, and comments upon the absurd distrust of theory which he found prevailing in Britain. Ogston called the merest routine practitioner a bold speculator and imperfect observer of facts. He remarks that the limits of pure observation in medicine are soon reached and discusses in separate chapters the inductive or analytic method as opposed to the deductive or synthetic method, rightly holding that the latter is a much more important concern of medicine than the former. Under the inductive or analytic method Ogston considers the processes of observation, comparison and analogy, and the numerical method. Under the deductive or synthetic method he considers first the process of analysis for deductive purposes, then the process of ratiocination and of verification. He discusses, among the processes subsidiary to induction, such matters as simple observation, experiment, hypothesis, analogy, the numerical method, terminology and classification. Ogston denounces the current nosologies as obstructive and inelastic and devotes special attention to what he calls the fallacies of nonobservation as opposed to the fallacies of malobservation. Much of this suspicion of Ogston can be traced in Oesterlen and Sir Gilbert Blane, to say nothing of their masters in logic, John Stuart Mill and Sir Francis Bacon.

Sir Gilbert Blane had, for example, in 1819 spoken of the sources of error in medicine as (*a*) the fallacy and danger of hypothetical and theoretical reasoning as especially demonstrated (according to Blane) in Boerhaave, (*b*) the diversity of constitutions, (*c*) the difficulty of "appreciating the salutary efforts of nature and of discriminating them from the operations of art," (*d*) superstition, (*e*) the ambiguity of language, and (*f*) the fallacy of testimonial.

Much can still be gained, no doubt, from a perusal of such works as those of Sir Gilbert Blane, Oesterlen and Ogston, and still more could doubtless be gained by the physician from a close study of John Stuart Mill and his predecessors in pure logic, but these studies were almost wholly given over with the onset of the evolutionary theory in the late fifties, with the crowding developments of pathology and physiology and especially of the bacteriology of the eighties and the immunology of the nineties of the last century. There has, in fact, crept over us the feeling that logical method is an inheritance of us all in like degree and that whatever we do not know of logic at the outset of medical practice we shall never learn. It is precisely the popular single volume textbooks that fail to yield much of practical value to the medical student seek-

ing to perfect himself in the *logic* of diagnosis. The dictum, especially of Da Costa and of his successors in the manufacture of single volume textbooks, namely, that the art of medicine consists in observation, has apparently abolished the necessity of logic. Carried away by the magic of this word "observation," many authors of physiologic works dealing with the most intricate discussions and fine-drawn conclusions cheerfully called their inductions and deductions by the term "observations." The obvious fact is that diagnosis does not consist in observation at all. Diagnosis requires observation, proceeds upon a basis of observation, but is in itself a process of combination, of reasoning, of calculation, or of some higher kind of intellectual process which takes observation for granted, uses and chooses amongst observations, but in no whit makes them.

Amongst the methods tabulated above I have first set down, following many of the books, *diagnosis by inspection*. Here, at the outset, it may be inquired: "Are we not terming a method of diagnosis what is nothing but a method of observation?" This I freely concede. The names of diseases are achieved by a process of inspection. The result is what we term a diagnosis, but the process by which the so-called diagnosis or disease-name is arrived at is not a process of reasoning at all, but (as stated above) a process akin to the statement, *It is raining*, or *The engine is skipping*. In short, no process of diagnosis in the logical sense is here being used. A diagnosis or disease-name is achieved, but reasoning is not employed. It is only, then, by courtesy that we include inspection under the process-types. The diagnosis follows the inspection as night follows day, or as black follows white, or as man follows woman. The process is one of association of a perfectly simple type. This kind of so-called diagnosis can be made by laymen often as well as by physicians. I am afraid that the ideals of many medical teachers, as they are got by the eager students, consist in teaching them thumb rules of inspection rather than the more tedious and complicated methods of diagnosis. I recalled above how Da Costa spoke of diagnosis by exclusion as a tedious method.

The second method tabulated above is one that I have presumed to term the method of *diagnosis by expectation*. We are familiar with the so-called expectant treatment in therapeutics, but, so far as I know, attention has not been called to the method of diagnosis by expectation. This is, of course, particularly employed in the fulminating, acute diseases on one hand and the chronic diseases on the other. In the one instance there may not be facts enough to permit a diagnosis by inspection and there may not be time enough to permit elaborate comparisons; accordingly, diagnosis goes by the board until an autopsy either is or is not made. As for the slow, hesitating course of certain diseases, the Micawber attitude is still easier to assume.

I suspect that the method *by induction* is commonly employed in a manner not far removed from the process of expectation. This method by induction, unlike the method by expectation, is mentioned in the classical works, and also in the modern work of Bieganski. One concludes that the patient looks tuberculous. Here is the suggestion of a diagnosis by inspection. Perhaps one is an office practitioner and time forbids exactitude. One examines the pulmonary

apex and discovers suspicions of dullness. One requests the sputum and proceeds to a positive diagnosis of tuberculosis on the basis of tubercle bacilli found in the sputum. Here is a successful case of diagnosis by induction by a sort of skipping of intermediaries (to use James's phrase) and by the least possible work. If the diagnosis is successful, well and good! If unsuccessful, one must proceed to more elaborate methods. It is always possible, too, that the patient may have been suffering from a combination of two or more diseases and that the tuberculosis e. g. found may be the lesser of two important conditions. One ought not, and I do not, condemn this method by induction just because it is not time-consuming and just because it does not succeed in all cases. In the hands of the expert the method of diagnosis by induction (as the phrase is here used) and the method of diagnosis by inspection are highly commendable methods. In a pragmatic age one ought not to denounce them. From the standpoint of a medical student, however, it would seem wise not to dazzle him with the brilliancies of inspection and induction (in the above narrow sense), but one ought to expound to him the nature of the more complex methods which he must often use in cases that are themselves at all complex.

The methods of *diagnosis ex juvantibus* and *ex nocentibus* tabulated above are in a sense experimental methods of diagnosis on all fours with the method by induction. The diagnosis of syphilis by the administration of antisyphilitic drugs and the procuring of a cure or an alleviation of symptoms is an example of diagnosis *ex juvantibus*. The provocative Wassermann reaction upon the administration of salvarsan is an example of the method of diagnosis *ex nocentibus*. It would be a mistake to consider the administration of drugs for these purposes therapeutic. The methods are methods of diagnosis purely.

Dismissing the methods of inspection, expectation, induction, *ex juvantibus* and *ex nocentibus*, we come to the methods of *diagnosis by comparison*, to which I hope to point out a small addition or modification which I conceive to be of value. Earlier in my communication I have sufficiently discussed these methods and I pointed out the necessity under which we labor of using the method of diagnosis by exclusion in cases where there are no indicator symptoms or presenting symptoms (to use Cabot's phrase for certain indicator symptoms). I wish to illustrate this method of *diagnosis per exclusionem in ordine* from the field of mental diseases, rehearsing the main groups of a practical key[24] which has been built up on the basis of Psychopathic Hospital data.

In passing, I may say that psychiatrists are far more at one in the matter of diagnosis than the general medical man is apt to believe. The unanimity in point of view is far greater than one would suspect from certain nomenclatural differences. The nomenclature of psychiatry is by no means as fixed at the present writing as the nomenclature of dermatology. Yet the unanimity of psychiatrists concerning the major groups of mental disease is, I make bold to say, almost as great, if not quite as great, as the unanimity of dermatologists concerning their main groups. The specialists in psychiatry have for some years past been much interested in proposals of the American Medico-Psychological Association to secure a thorough and acceptable classification of mental diseases to which the State institutions for the custodial insane could conform. The

classification adopted by the Medico-Psychological Association in 1917 is, in general, a highly acceptable one.[25] Probably no member of the committee charged with making the classification is entirely satisfied with it in details. Some diagnosticians go so far as to say that in the interest of the patient no classification in the sense of the statistical tables of institutions is worth while, since every instance of mental disease is virtually *sui generis*. There is, of course, much truth in this contention, and the good therapeutist never forgets this fact, borne in upon the mind as it is by the tremendous individual variety of the psychogenic reactions of the individual as such. I found that most of the leading American textbooks of psychiatry were also practically at one in the major categories, despite perturbing difficulties in terminology.

The task of the Psychopathic Hospital, dealing as it does not merely with custodial insane but with all the penumbra of "near-insane," of incipient, mild and curable cases, and with many psychoneuroses which would not ordinarily be classed among the insanities, is a somewhat broader and deeper task in diagnosis than that of the custodial institutions for the insane. The Psychopathic Hospital stands as a sort of vestibule between the community and the custodial institutions. From its meshes go back into the community numerous cases whose psychopathia is not far advanced enough to go through the interstices. Not only insanity in the narrow sense, but a variety of other conditions of the *non compos mentis* group, namely, feeble-mindedness, epilepsy, and even many forms of alcoholism come within the purview of the Psychopathic Hospital. The task of rapid diagnosis was one which had never faced the custodial institution for the insane, because to the latter flowed only cases in which diagnostic experts had made their decision outside the walls of the institution and with the concurrence of the Courts. It became necessary, therefore, to contrive more rapid methods of handling cases than had formerly been available, inasmuch as keen and mature experts were not available for the great run of cases (the Psychopathic Hospital ran the number of voluntary cases and of so-called temporary care group of cases up by the hundreds as soon as it was founded). Some provision had to be made whereby younger men could make reasonably accurate primary siftings of the cases. The rapid development of mental hygiene stole away the young men at such a rate from our staff that provision had to be made for shifting staffs of relatively inexperienced persons. The situation was not unlike that which faced the army itself at the outset of the first draft.

Mental diseases have no indicator symptoms, barring a few, and indeed a very few, so-called pathognomonic symptoms. Psychiatry was devoid of pointers, such as would be available to the specialist in the exanthems, for example. In the absence of indicator symptoms, some method had to be chosen by which every case would have every major hypothesis concerning its nosological grouping raised at some time during his hospital stay. The legal details and official regulations were such that these hypotheses had to be raised within a very short period. Early in our experience the laws and regulations were such that some kind of diagnosis permitting proper disposition of the case had to be made within four or five days. This proved to be too brief a period in

which to make proper disposition and the Temporary Care Law, under which the majority of Psychopathic Hospital cases are admitted for observation directly from the community (without court process), was modified so that a period of seven or eight days is now available. Official disposition is at present made in a total period of ten days, instead of in a total period of seven days; but in practice the external conditions of transfer to social adjustment take from two to three days, so that the total time available for group diagnosis is now a period of from seven to eight days. During this period of seven to eight days what can be done?

I assume that in private practice it may not be necessary to secure the Wassermann reaction of the serum in each and every mental case. For my part, I never feel certain of the diagnosis unless this precaution is taken. In any event, in Psychopathic Hospital practice, with the varying conditions of staff and history standard, it shortly proved necessary to get the Wassermann data from the serum in each case. Only a few of the more conservative hospital superintendents failed at first to approve this plan. The Danvers Hospital in Massachusetts and the hospitals in Michigan, under the influence of the Psychopathic Ward at Ann Arbor, had early adopted doing the Wassermann reaction of the serum as routine. Upon reflection, I found that the proper disposition of almost each and every case depended upon our securing this Wassermann data. If the Wassermann data were dubious, then a longer period of diagnosis was necessary. If the serum proved negative but there were other signs of organic disease of the nervous system, lumbar puncture was resorted to, with the diagnostic hope that the Wassermann reaction and the other reactions of the fluid would prove decisive. The practical disposition of each case I found to depend upon taking the Wassermann reaction of the serum. Accordingly, although there is no indicator symptom which is infallible or anywhere near infallible in the detection of neurosyphilis, the value of the Wassermann reaction of the serum is such that I feel entitled to place the syphilopsychoses, or mental diseases of syphilitic origin, at the head of all diagnostic consideration. This was the beginning of the plan of ordinal exclusion, the plan of diagnosis *per exclusionem in ordine*. The first thing to be excluded in the diagnosis of mental disease was, in short, syphilis.

The second thing to be excluded was, I found in practice, some form of feeble-mindedness. To be sure, the obvious imbeciles and idiots may secure their diagnosis by inspection, and not so much difficulty is ordinarily felt amongst the morons or the feeble-minded proper of the English classification. But when one came to the so-called stupids or subnormals, that we now find to lie between the morons below and the normals above, the value of the Binet-Simon tests or their analogues became extreme. One does not need to claim one hundred per cent values for these tests any more than for many another biological test. The tests are nevertheless of value. I found that in practice I needed to know for every lucid case, that is, for every case which could practically be tested metrically, the intellectual titer. Even were I dealing with such a condition as dementia precox or manic-depressive psychosis, I nevertheless found that I needed the mental test as a base line.

Thirdly, I found that the hypothesis of epilepsy or epileptic symptoms and of epileptoid phenomena is one very apt to be isolated from consideration by the tyro or even by the expert. I placed epilepsy third in the diagnostic order of exclusion partly because of the relative reliability of the clinical histories in these cases.

After Group I, the syphilopsychoses, Group II, the hypophrenoses (feeble-mindednesses), Group III, the epileptoses, Group IV, the pharmacopsychoses (including mental diseases due to alcohol, drugs and poisons), I come to Group V, the group of mental diseases due to focal brain disease,—the so-called encephalopsychoses. This is the group of cases in which we unconditionally need the data of the routine neurologist's diagnosis. We need to exclude conditions of heightened intracranial pressure and conditions of asymmetry, reflexes and the like, indicating focal brain disease.

Sixthly, after Group V, the encephalopsychoses or neurologist's group, I found that in practice I was asking for the data of the internes, namely, the data which would go to make a diagnosis of a mental disease somewhere in the "symptomatic" group,—Group VI, a group I have termed the somatopsychoses.

After these I tried to exclude presenile and senile phenomena belonging in a group which I have termed, following Nascher's Geriatrics, the geriopsychoses (Group VII).

Then come the stock difficulties of diagnosis for the psychiatrist,—the diagnosis of Group VIII, the dementia precox group, which I like to term (from their main symptom as defined by Bleuler) the schizophrenoses.

After the schizophrenoses stand Group IX, the cyclothymoses, or a group including the manic-depressive psychoses and similar mental diseases.

The last of the ten well-defined groups is the familiar group (X) of the psychoneuroses including the hysterias, neurasthenias and psychasthenias, but if in the diagnostic order of exclusion one could not place one's case in any one of these ten comparatively well-defined groups, one would not throw it altogether out of the psychiatric lists, but would call it a plain psychopathia and put it in Group XI, the psychopathoses. A table of these major groups is shown on the following page.

I have spoken of the botanical and zoological analogues of this grouping in a paper read before the Neurological Association in 1917. Two words of warning are necessary concerning this analogy. The choice of the ending *osis* is obviously an attempt to get a medical analogue for the botanical ending *-aceae* or *-osae*, as in the orders *Rosaceae* and *Leguminosae*. These botanical orders are, as is well known, susceptible of splitting into genera and species. It would be an entirely superficial objection, for this account, to say that the term "species" has obtained in natural history a very special meaning which could not appropriately be given to a disease. Biologically speaking, a species is sometimes taken to mean such a group of plants or animals as are capable of breeding true to type. However, the genus-species distinction is a great deal older than natural history and is used throughout every province of logical

classification known. For example, the mineral kingdom, though without process of breeding, is in part susceptible to a classification of the genus-species sort. For that matter, it is not necessary to use the terms order, genus and species for these groupings at all. One might use entirely other distinctions, and still the process of classification might be entirely valid.

The other point which should be made is a kindred one. In zoology and botany one would ordinarily be satisfied if in the process of logical exclusion one arrived at the animal or plant which fulfilled the conditions of differentiation, but in the process of diagnosis *per exclusionem in ordine* as applied to mental disease one unconditionally needs to go through the entire list in each case.

For example, one might easily face an instance of mental disease such that the victim was a syphilitic, feeble-minded, epileptic, alcoholic old man, with focal brain disease and somatic disease, the whole contributing to his mental picture. He might conceivably have been psychoneurotic or cyclothymic in

MENTAL DISEASE GROUPS (ORDERS)

1. Syphilitic	Syphilopsychoses
2. Feeble-minded	Hypophrenoses
3. Epileptic	Epileptoses
4. Alcoholic, drug, poison	Pharmacopsychoses
5. Focal brain ("organic," arteriosclerotic)	Encephalopsychoses
6. Bodily disease ("symptomatic")	Somatopsychoses
7. Senescent, senile	Geriopsychoses
8. Dementia precox, paraphrenic	Schizophrenoses
9. Manic-depressive, cyclothymic	Cyclothymoses
10. Hysteric, psycho-, neurasthenic	Psychoneuroses
11. Psychopathic, paranoiac, et al	Psychopathoses

his life, for these conditions are doubtless consistent with a fundamental feeble-mindedness in some cases. Whether he could also have been a victim of schizophrenia (dementia precox) and still have mental phenomena attributable to all these other groups is a question. We are aware of cases that start by being feeble-minded and apparently have their schizophrenic process grafted upon them; but whether these combinations of psychoses in so multiplex a form are common or really exist is not my point. Combinations of two or three of these conditions are not infrequent. It is, therefore, stringently necessary, in the rough analysis of psychiatric cases, to make all of these major hypotheses and dismiss them or fix upon them one by one. In short, diagnosis *per exclusionem in ordine* does not necessarily exclude ten out of the eleven groups, but it does endeavor to exclude each one of at least ten of the groups. If the process has succeeded in excluding the first ten, the case, if psychiatric at all, must remain in the unresolved or ragbag group of psychopathias, Group XI, the psychopathoses. I do not intend here to enter the minutiae of psychiatric diagnosis, although in another place I have made some endeavor to describe the main genera and species of the groups above tabulated.[26] Incidentally, I have endeavored to place genera and species in the same sort of practical order so that the tyro may consider the diagnosis

of the species of syphilitic, hypophrenic and other forms of disease in arbitrary order.

It is scarcely necessary for me to insist that I do not attach great consequence to there being ten or eleven more or less major groups of mental disease. In fact, I insist that the future must interpolate or extrapolate these groups. The groups are not groups based upon clinical resemblances alone, upon anatomical disease, or upon etiology. They are practical groups devised upon what has been found to be the best practical order of exclusion of major groups of mental disease, each seeming to require a special form of handling. I have described the method in my paper entitled "A Key to the Practical Grouping of Mental Diseases." I am not sure that I would not be warranted in using the term pragmatic instead of practical, for the end and aim of these groupings is, after all, a therapeutic one. The basis for these rough distinctions is a question of disposal of the patient. If the patient belongs amongst the syphilopsychoses, then antisyphilitic therapy is indicated, or at least must be thought of. If the patient is hypophrenic, then a school for the feeble-minded, an institutional equivalent, or some form of supervision looking to the safeguarding of the community and the development of the case must be adopted. If the case is epileptic, certain special safeguards are necessary, whether the case is an alcoholic epileptic or a traumatic epileptic. The etiology and the anatomy are not at all so much to the point as the practical handling of the epileptic. So, too, with the alcohol and drug cases. In fact, the practical consequences of placing one's patient in one of the first four groups of syphilitic, hypophrenic, epileptic and alcohol or drug cases are such that I think on these practical grounds alone it would be wise for the diagnostician to consider syphilis, feeble-mindedness, epilepsy and alcohol, drugs and poisons before he comes to the minutiae. He will thus get settled in his mind many of the practical social questions of a legal, institutional and social service nature. Take the group of mental diseases due to focal brain disease. Should the phenomena of the present war show us that the traumatic psychoses, that is, psychoses due to structural brain disorder, form a practical group on a level of practical interest equal to that of the listed groups, I for one should have no objection to raising these traumatic psychoses, which I at present place under the encephalopsychoses, to a higher dignity, namely, that of the traumatopsychoses. For the moment, I seem to feel, and I suppose most of my colleagues would agree with me, that the traumatic psychoses rather resemble genera under the focal brain disease group than the true great orders of disease. Let the list be telescoped or accordeonized as you will, no damage is done to the concept-value of the greater groups of mental disease.

Again, should someone wish to consider the somatopsychoses ahead of the focal brain disease group and exclude e. g. pellagra and cardiorenal disease from a role in the given patient ahead of brain abscess, brain tumor, arteriosclerosis, and the like, I should have no objection. The point I make is that some order, not any particular order, is desirable for the tyro in diagnosis. I insist, therefore, on no particular great groups, but on the principle that

there should be great pragmatic groups of mental disease analogous to the orders of botany. I insist, again, on no particular order of exclusion, but on some order of exclusion of these groups, and above all, I insist upon subjecting each mental case, so long as indicator symptoms are so woefully absent, to the hypothesis of his possibly belonging under every one of these great groups. Indeed, I feel that he may belong in two or more of these groups.

Whither, you may ask, does the pragmatic principle then disappear? Suppose a man is both epileptic and alcoholic; shall we classify him as in the group of epileptoses or in the group of the pharmacopsychoses? All specialists will remember acrimonious discussions of this nature. Are we dealing with epilepsy or with alcoholism, or with both? Now, I find that in practice, if you couch the question pragmatically, there is rarely, if ever, any doubt into what group you wish to throw your case. Once you put the question thus: Do you wish to send this case to an institution for epileptics or do you wish to put him in an institution for alcoholics or under appropriate supervision suitable for alcoholics? There is almost never any doubt on the part of the careful physician whether his case is a case for an institution for epileptics or a case for an institution for alcoholics. The pragmatic question is forthwith settled. The academic question, whether one is an epileptic alcoholic or an alcoholic epileptic becomes a vividly practical question, when the pragmatic, that is to say, the therapeutic, question is raised. I find that this kind of consideration matures the tyro in psychiatry very fast.

SUMMARY

1. The writer apologizes for a communication on Medical Logic in general when he is only a psychiatrist and but recently a pathologist. His excuse is the necessity for reasonably accurate snap diagnosis in the sifting problem of the psychoses, psychoneuroses and psychopathias, as they flow through the Psychopathic Hospital clinic in Boston.

2. The medical student is found destitute of the ability to define entities and symptoms. The textbooks in medicine, especially the single volume textbooks, rather tend to make the student believe that diagnosis is observation. In point of fact, diagnosis is not observation, though it requires and indeed stands or falls by accurate observation.

3. Da Costa and his successors have lauded so-called direct diagnosis to the skies and Da Costa rather decried indirect diagnosis by exclusion as a tedious process. An example is cited from Da Costa which shows how relatively simple the classical diagnoses of general medicine are beside those of psychiatry.

4. It seemed that diagnosis by exclusion ought to be rehabilitated. An examination of recent research work in logic indicated that higher and more complex methods than those of observation had become necessary in science. For example, Cabot and Herbert French have attempted to profit by the statistical method, which again, though it requires reasonably accurate observation, is not in itself a method of observation at all. Yet Cabot's statistical fre-

quency tables possess a certain diagnostic value. But the student is often misled by the brilliancies of so-called observational diagnosis in a clinic. Here diagnoses are often rendered on inspection by a process akin to the recognition of a fruit as an orange, or an automobile trouble as "the engine is skipping." This process is not diagnosis, it is a process of recognition that may receive a simpler term *gnosis*.

5. The offhand snap diagnostic work at the Psychopathic Hospital indicated that we were in practice relying upon the successive exclusion of certain great disease groups in a certain definite order.

6. A study of Royce's "Summary of Recent Researches in Logic" shows how an organized combination of theory and experience is the higher logic to which the more complicated sciences must resort. Royce himself mentioned psychiatry as a science about to climb out of the classifying era into the era of logical order, that is, of the organized combination of theory and experience. Such a dictum that "disease is life under altered conditions" appears now childishly simple. The idea that disease is a matter of an organism plus a germ was found to be altogether too simple when in the nineties of the last century the concepts of immunology were developed.

7. Those departments of medicine in which the presenting symptom of Richard Cabot is of value are lucky departments. Those departments of medicine in which the indices of disease, or indicator symptoms of the elder writers are available, are also fortunate departments in comparison with psychiatry. In mental disease there are exceedingly few indicator symptoms.

8. Hence the need became apparent of a process of exclusion of great groups or phenomena in a certain definite order, so that nothing of large significance should evade consideration. To avoid the tediousness of exclusion, complained of by Da Costa, the phenomena of disease had to be logically grouped in certain great groups, and the process types of diagnosis in the books may be counted as six or eight, according to definition.

9. In the body of the paper, a special statement was made about each of these process types: Inspection (regarded as not really diagnosis but as merely recognition of gnosis). Expectation, a newly named but frequent method (far older than Micawber). Induction, *Ex juvantibus*, *Ex nocentibus* (three methods in which in no very rigorous way experiment is used) and three methods of diagnosis by comparison are successively discussed.

10. The ninth method, diagnosis *per exclusionem in ordine*, is in one sense a minor modification of the old method of diagnosis by exclusion. It is of value in departments of medicine where there are no indicator symptoms, and where the so-called presenting symptom would merely indicate some kind of mental disease.

11. The general application of the method of diagnosis *per exclusionem in ordine* in the field of mental disease is demonstrated in the eleventh group of mental diseases into which most of the phenomena may be pragmatically cast. The groupings are not by clinical resemblances, by anatomical attack or by etiology. The distinction is a pragmatic and therapeutic one and will naturally

tend to become more and more etiologic as the causes are determined. But in the field of mental disease, causes are so apt either to be unknown or to be multiple that etiologic classification on any simple basis such as that of the infectious diseases is practically inconceivable.

12. It is hoped that other departments of medicine (where diagnosis is raised above the level of mere recognition) and where there are few or no pathognomonic or indicator symptoms, will find it to their advantage to set up a method of diagnosis *per exclusionem in ordine*, the great groups or orders being always determined on a pragmatic basis. In the body of the paper are given the general designations of the ten great groups of mental diseases, with the eleventh residual group.

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THE BACILLUS INFLUENZÆ IN SINUSITIS AND MENINGITIS*

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SINCE the discovery by Pfeiffer of the Bacillus influenzæ during the influenza pandemic of 1892, a great deal of work has been published showing the presence of this bacillus as the probable etiologic factor in a number of the sequellæ of clinical influenza and other allied conditions. Pfeiffer's work is well reviewed by Scheller,[1] in which he gives an excellent resumé of all that was known of the organism up to that time. Pfeiffer was able to demonstrate the Bacillus influenzæ in the sputum of a large percentage of his cases of clinical influenza during the early stages of the disease but during the later stages it had disappeared entirely. Davis[2] has more recently (1908) reported forty-one cases of clinical influenza in which his findings were quite at variance with those of Pfeiffer, in that he was unable to demonstrate the organism in the sputum of but seven of his forty-one cases, and that in these he found the bacilli only during the later stages of the attack. The earliest he found them was on the fourth day, the average time being much later.

Of greater interest perhaps, than the presence of Bacillus influenzæ in the sputum, is its presence in the accessory sinuses of the respiratory tract and in the spinal fluid of cases of influenzal meningitis. During the last year two instances of sinusitis without meningitis and two which were followed by meningitis have come to our laboratory. I shall make these the basis of this report.

CASE HISTORIES

Case I.—*Influenzal Meningitis.*—Baby S. Male. Age ten months. Patient of Dr. D. H. Boyd. Children's Hospital, Pittsburgh. The patient though still well nourished showed evidences of rapid loss of weight. Family history and past history negative. The patient was brought into the hospital April 24, 1917, in an unconscious condition. The present illness had begun about four weeks before with pain and swelling of the right knee, followed two weeks later by pain and stiffness in the shoulders. There was slight improvement until two weeks later when he became irritable, began vomiting and was unable to retain his food. Physical examination on entrance to the hospital showed that the patient remained in any position in which he was placed, with eyes turned toward the right. Every evidence of meningitis was present except a positive Koernig. Further physical examination was negative except for slight dullness and increased breath sounds both anteriorly and posteriorly over the right lung more marked at the base than elsewhere. A few moist rales were also present. A diagnosis of meningitis was made. Lumbar puncture yielded 40 c.c. of turbid spinal fluid under pressure. The cell count was 276 per c.mm. and smears showed several organisms which appeared to be gram-negative cocci, some seemed to be in chains and were not typical of meningococci. There is no record of cultures having been made on the spinal fluid during life. Daily lumbar punctures showed the same type of fluid until death occurred on April 27, 1917. The body was brought to the Singer Laboratory for autopsy.

Autopsy Report.—Autopsy (Drs. Plumer and Allison). The body was one of a well-developed and moderately well-nourished white, male child apparently about one year old. The pupils were unequal, the abdomen was retracted and the right knee was swollen. No other unusual conditions were noted externally. The thymus gland was relatively small. The other thoracic and abdominal organs were greatly congested and otherwise

*From the William H. Singer Memorial Research Laboratory, Pittsburgh, Pa.

appeared negative. The important pathologic changes were contained within the cranial cavity and spinal canal.

Brain.—The dura was distended from internal pressure. The cerebrum was covered with a yellowish fibrinous exudate which formed a part of a membrane extending more or less completely over all of the brain surfaces. Over both upper and lower surfaces of the frontal lobes the membrane was so thick and shaggy that the vessels were entirely obscured. The Sylvian fissures were completely filled with the exudate. Over the parietal and occipital lobes the membrane was not so thick and the greatly congested pial vessels stood out prominently. About the optic commissure and infundibulum and over the cerebral peduncles, pons, medulla and lower surfaces of the cerebellum the exudate was again very thick. The left lower cerebellar surface was covered with a somewhat thicker layer of fibrin than the right and the superior surfaces of both cerebellar lobes were practically free. The general appearance and the boggy feel of the cerebrum suggested the

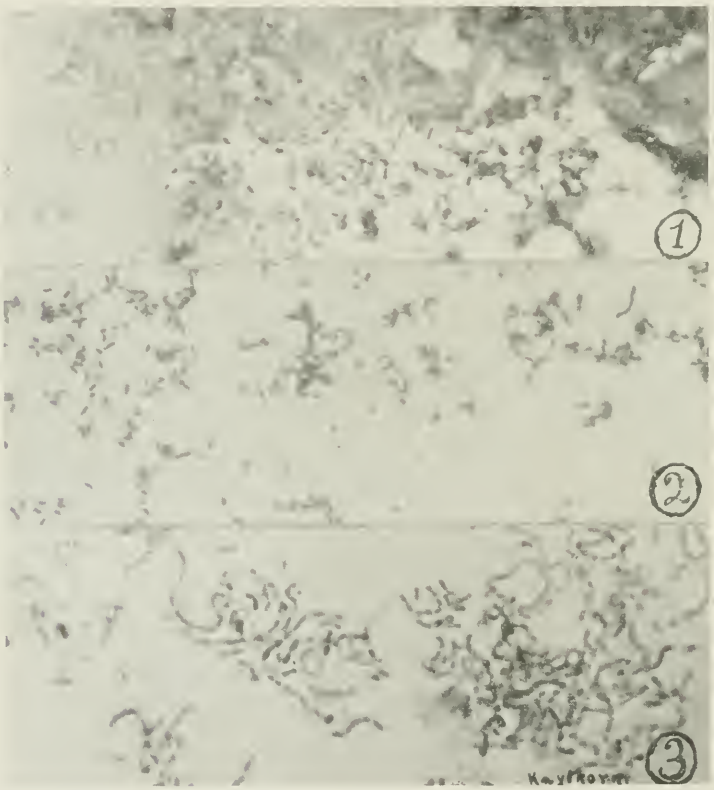

Fig. 1.—Direct smear of sputum showing influenza bacilli. 2. Forty-eight-hour culture showing early division forms and spirals. 3. Seventy-two-hour culture showing filamentous involution forms.

presence of fluid in the lateral ventricles but the brain was placed unopened in a hardening fluid. The cord was covered with a similar membranous exudate. Both middle ears contained yellow pus.

Microscopic Description.—Microscopically the meninges were seen to be covered with a sero-fibrino-purulent membrane of varying thickness. All of the sections showed the presence of an abundance of fibrin which was of the filamentous nonhyaline type, the strands of which were widely separated by serous and cellular exudate. In the thicker portions the cellular elements predominated with a high proportion of polymorphonuclear cells; many plasma cells and phagocytic endothelial cells also being present. A few short gram-negative bacilli were made out. These were both intra- and extracellular. The smaller vessel walls were swollen and infiltrated with leucocytes. The connective

tissue cells of the pia were swollen and edematous. The brain substance proper presented no evident changes beyond a marked edema.

The lungs were edematous and the bronchioles were filled with an acute exudate, which was composed chiefly of leucocytes and fibrin and which contained very small gram-negative bacilli and a few other bacteria. The kidneys showed marked tubular degeneration, congestion and edema. The other organs were not remarkable.

Bacteriological Report.—Direct smears from meningeal exudate were negative. Cultures were taken at autopsy from the cerebrospinal fluid, lepto meninges, base of the brain and from the middle ears. The middle ears and the meningeal cultures contained a predominance of very fine short gram-negative bacilli, which at first were difficult to distinguish from diplococci. This organism was also found in pure culture in the spinal fluid. It grew only on blood agar and required forty-eight hours for its development. Since it was recovered in pure culture from the spinal fluid at autopsy it is reasonable to assume that it was the same organism which was found in the spinal fluid before death. This organism was in every respect identical with the influenza bacillus. There were a few gram-positive cocci recovered from the meninges and also from the mastoid cells. These were staphylococci and were perhaps a contamination from opening the cranial cavity as they were only very few in number.

Case II.—*Influenzal Meningitis.*—Baby H. Patient of Dr. L. C. Fausold. A well-nourished male child ten months of age. The father said that the child had been strong and well until a short time before the present illness when it developed a cold which lasted several days and was followed by a profuse discharge from the nose and from the left eye. There was also a marked swelling developed over the region of the left maxillary sinus. These had subsided somewhat when the patient (November 21, 1917) began to show signs of meningeal irritation. By the twenty-third definite symptoms of meningitis were present. About 30 c.c. of cerebrospinal fluid was withdrawn by Dr. Fausold who stated that it was under great pressure. The fluid was very turbid, so much so that a heavy precipitate had formed in the bottom of the tube by the time it was received at the laboratory. A cell count was not made on account of the extreme turbidity. Direct smears were made from the sediment and stained by Gram's method, which showed the cells to be practically all of the polymorphonuclear type. Throughout each microscopic field extracellular and occasionally intracellular gram-negative bacilli were found which varied greatly in size. The majority of these bacilli were slightly larger than the average influenza bacillus and gave the appearance of the leptothrix group of organisms. Cultures of this organism proved to be a pure culture of Bacillus influenzæ. Lumbar punctures were done daily for several days giving temporary relief and the spinal fluid became much less turbid. The patient appeared greatly improved for about a week or ten days but became very much worse and died December 5, fourteen days after development of symptoms. Pure cultures of the same organism were recovered from the fluid obtained at subsequent punctures.

Case III.—*Frontal Sinusitis.*—Mr. H. C. Patient of Dr. Robert Milligan, Allegheny General Hospital. A young white man, twenty-three years of age. Occupation, engineer. Family history and past history negative. Present illness began in February, 1917, with an attack of grippe. This lasted several days and after he was up he noticed a swelling over his upper right eyelid. This became very painful and his physician incised it. A large amount of pus was evacuated and continued to drain through the incision, so that a sinus was formed. He finally sought the services of an ophthalmologist and was treated with injections of silver nitrate without benefit. On July 7, 1917, the sinus was curetted and some pieces of necrotic bone removed. The discharge continued and he was transferred to the service of Dr. Milligan in September. Attempts were made to institute drainage from the frontal sinus through the nose by doing, first a turbinectomy and later a high submucous resection of the septal plate. These methods each failed to relieve the condition and on November 6 the discharging sinus was incised, the anterior wall of the frontal sinus removed, thorough light curettage done, the wound packed and drainage established both externally and through the nose. The discharge remained very profuse despite the fact that the wound was being irrigated two or three times daily alternating with a weak solution of potassium permanganate and distilled water. A culture was made at this time which showed almost pure culture of Bacillus influenzæ with an occasional colony of hemolytic streptococci. A vaccine was prepared from this and given at four-day intervals. It produced a rather severe local reaction especially after the first few injections. There was decided improvement in the patient's general condition and lessen-

ing of the discharge after the second injection. Although there was still a slight amount of discharge from the wound it was improving and the patient was dismissed from the hospital December 19, 1917. At that time cultures from the pus were negative for Bacillus influenzæ.

Case IV.—*Frontal Sinusitis.*—Patient of Dr. Milligan. Allegheny General Hospital. A white man, aged thirty-two years. Occupation, toolmaker. Family history negative. Past history negative except for an apparent susceptibility to colds, which he had had three or four times during the last year. The patient says that two years ago he began to have pain over the left side of the face; he had a tooth extracted but this failed to give relief. Since that time the pain has been intermittent. The pain would start at the inner canthus of the left eye and spread over the left side of the face and head. Nothing had been done surgically to relieve the condition, but he had seven years previously had a submucous resection of the nasal septum on the left side. During the past few months he had had the frontal sinus probed through the nose several times in an attempt to establish thorough drainage through this route. Each probing was followed by prompt relief but it was only temporary. On November 20, 1917, an incision was made over the left superciliary ridge, a trephine done and a small portion of bone forming the anterior wall of the frontal sinus was removed. Light curettage of the frontal sinus was done, the anterior ethmoid cells opened and the superior turbinate and bulla ethmoidalis removed and a gauze drain passed down through the opening thus formed. The external wound was closed and the drain allowed to remain in position two or three days. No further local treatment was given except necessary dressings. A culture taken from the frontal sinus at operation showed a predominance of Bacillus influenzæ with a few staphylococci and streptococci. A vaccine was prepared for this patient and given as in Case III, but the results were not so encouraging.

The bacteriological findings in these four cases were interesting in that they represented two different types or forms of the Bacillus influenzæ. First, the small short "textbook" type and second the long filamentous or streptothrix-like forms called by Pfeiffer "scheinfädenbildung" or involution forms. Attention has also been called to these two forms by Wollstein,[3] Henry,[4] Ritchie[5] and Bhat.[6] Wollstein states that the shorter forms which she used were obtained from the sputum of influenzal patients and the longer forms from patients with influenzal meningitis. She found the long ones to be of much higher pathogenicity than the shorter ones.

In the four cases reported above, the short forms were isolated from Cases I and IV and the longer ones from Cases II and III. In each of the first three cases it required forty-eight hours for the development of the characteristic pin point or dewdrop colonies on blood agar while in the last case they developed in twenty-four hours. This latter occurrence may have been due, as others have suggested, to the presence of the streptococcus and staphylococcus associated with the Bacillus influenzæ. A point against this is that after it had been isolated in pure culture the growth was equally as rapid. All of the cultures showed a tendency for the colonies on blood agar to remain discrete. Each failed to grow on any of the ordinary media except blood agar and litmus milk, the latter being alkalinized in about six or seven days. The short forms in Cases I and IV retained their original morphology as long as they were kept on culture media, which was for a period of several weeks. There was no tendency toward the formation of the longer or involution forms. The shorter forms predominated in Cases II and III when the cultures were first isolated, but after the first transfers the long filamentous forms began to appear and were soon in the majority with only a few of the short ones remaining. It was noted that these long filaments were generally found on the lower part of the culture tube near the water of condensation, which suggested that the moisture of the media might have some effect on their production. Transfers were therefore, made from a culture containing the long type, to blood agar which had been well dried for several hours in a paraffin oven. Colonies developed on this medium in forty-eight hours as on the fresh moist medium but smears from these showed the bacilli to be practically all of the short variety. Transfers to the moist blood agar showed a return to the long filamentous forms, showing fairly conclusively that we were dealing with two phases of the same organism and not with different organisms. There seems to be a definite relationship between the development of influenzal meningitis and infections of the frontal and maxillary sinuses and mastoid cells, a point previously mentioned by Cohoe[7] and Ritchie. In one of our cases the meningitis was preceded by an infection of the mastoid cells and in the other by an infection of the maxillary sinus.

SUMMARY

In all cases of meningitis, either mild or severe, of indefinite etiology it is advisable to centrifuge the spinal fluid and culture it on various media, always using blood agar. Observations on this should be made for at least forty-eight hours before a negative report is made.

The presence of gram-negative bacilli in direct smears or on cultures from cerebrospinal fluid or from the accessory sinuses of the respiratory tract should be looked upon as probable Bacillus influenzæ. This is especially true when long filamentous forms are present.

There are probably two types of Bacillus influenzæ as suggested by the cases reported here; the one which retains its original short bacillary form indefinitely on artificial media and the other which readily develops filamentous forms after a few days on moist blood agar.

Sinus infections with the Bacillus influenzæ should have early and adequate drainage to prevent the danger of a complicating meningitis.

NOTE.—Since the completion of the above work,* Major H. E. Robertson of the American Expeditionary Force in France, has reported the recovery of B. influenzæ from the accessory sinuses of fourteen cases at autopsy: seven times out of eight, cases of influenzal tracheobronchitis; six times from patients dead from other infectious diseases; and twice from men dying of accidental causes. Major Robertson did not go into the cultural characteristics nor morphological differences of the bacillus. (S.R.H.)

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THE COMPARATIVE VALUES OF SOME LOCAL ANESTHETICS*

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NOVOCAINE, while conceded to be somewhat less effective in practice than cocaine, has gained a reputation for effectiveness which, taken along with its stability in solution when heated to sterilize, its lower toxicity, and its freedom from habit-forming effects, has made it second to none in its general applicability. While it is true that most of the defects of cocaine can be overcome by one means or another the disappearance of novocaine from the market has been generally regarded as a distinct loss.

A recent addition to the list of local anesthetics is apothesine, which has proved to be not merely a substitute for novocaine and cocaine but a product worthy of closest investigation. Unfortunately, in a series of experiments by Sollmann[1] in which he examined some of the most important local anesthetics this product was passed over as of minor importance.

The reason advanced by Sollmann for reopening an investigation of local anesthetics namely "the wish to select 'the best'" is sufficient reason for this publication, with the added incentive that while his work is apparently comprehensive, covering as it does the efficiencies of a number of substances by five different methods of valuation, the whole field is not fully covered, since apothesine is included in the tests of only two of the five series.

The first series of his experiments, and the first one appearing in complete detail,[2] is that describing the comparison of a number of local anesthetics on the sciatic nerve of the frog. One would assume from reading the first article that apothesine had not come to the author's attention.

In two subsequent test-methods, however, it is included—in the cornea test and in the intracutaneous test. Based on the results obtained by the first of these two methods he concluded that novocaine and apothesine are inefficient relatively to cocaine, although apothesine is 100 per cent more active than novocaine. In the intracutaneous test his results would indicate that novocaine is fully equal to cocaine while apothesine is only one-eighth as efficient.

Since Sollmann's experiments led him to conclusions radically different from those which we have observed the subject is reopened to include the comparison of apothesine with other anesthetics by three of the methods he applied and to point out what are evidently errors in his work.

As in Sollmann's paper this publication does not touch on the toxicity since there are different interpretations to be placed on results obtainable by almost any method. The important feature in this respect is that apothesine is only one-fifth as toxic as cocaine by subcutaneous injection into guinea pigs and that in relatively large doses no systemic effects have been in evidence. Local irritation, too, is a clinical problem and may logically be omitted from this discussion.

As to the relative merits of the different methods of examination of local

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anesthetics this too must be left to the ultimate judgment of the clinician. The use of a new anesthetic is necessarily governed by its relative efficiency, first of all as shown by laboratory tests but finally by observation of its action in practical use.

Among the laboratory tests that have been devised for investigation of local anesthetics there are three, each of which appears to have a very direct bearing on the clinical application of these substances, namely—the intracutaneous, comparable to infiltration anesthesia; the nerve trunk anesthesia, comparable to nerve blocking or conduction anesthesia; and surface anesthesia—the mucous membrane of the eye, nose and throat—reproduced by application to the frog's foot or to the cornea.

If the results of testing the different local anesthetics by the different methods agreed relatively, this would show that comparison by any one of the methods would give the relative efficiencies. That this is not true, however, is apparently shown by observing the varying ratios obtained by both Sollmann and ourselves. The laboratory results are therefore only suggestive, and do not absolutely demonstrate the clinical value of a local anesthetic.

In the following experiments the hydrochlorides of each of the local anesthetics tested were used in every case, no experiments having been conducted after neutralization. Experiments with mixed anesthetics were also omitted as having no direct bearing on the object of the paper.

MOTOR NERVE ANESTHESIA

The method most commonly used for testing the value of a local anesthetic where exact data is desirable, is to apply the anesthetic to the sciatic nerve of the frog, the nerve being separated at its point of branching from the spinal column. The objection has been made that this is a determination of motor nerve anesthesia only and no evidence of efficiency on the sensory nerves. It has been demonstrated, however, that the sensory nerves are the first to be anesthetized[3] and therefore a measure of motor nerve anesthesia is a fair indication that the sensory nerves are at least equally anesthetized. Objection has also been made that this method is very different from the practical use of anesthetics, but on this point, too, there are counterbalancing reasons which give the method practical value for measuring anesthetics. This test shows at once the nerve blocking value such as results from subcutaneous and subdural injections and as this is one of the uses of local anesthesia, its measurement is of primary importance. This method also meets one of the requirements of physiological testing in its accuracy of measurement, the exposed nerve can so easily be irritated to determine the degree of anesthesia when either the strength of solution or the length of time is the measuring factor. The accuracy of measurement is not affected by the factors which may affect the intracutaneous method, one of which is the pressure of the solution and another its character, such as tonicity, concentration, irritation, diffusibility.

As a sole method of valuing local anesthetics it would fail to give a true picture, but taken as one of several methods, especially along with that of subcutaneous administration the nerve blocking action is undoubtedly of primary importance and deserves especial consideration.

This phase of the subject has been so thoroughly covered by other investigators that no further description is necessary and only additional data or materially different results furnish an adequate reason for further publications.

While working with the intent to verify or disprove Sollmann's results the method followed was varied to the extent that no work was carried out with the high dilutions he employed, these having no practical bearing on the subject.

TABLE I

ANESTHESIA AS SHOWN BY RESPONSE TO CURRENT AFTER MINUTES

SUBSTANCE	DILUTION %	0	5	8	10	12	15	20	25
Cocaine	0.5	–	–	±	±	+			
		–	–	±	±	±	±	±	+
		–	–	±	±	±	±	+	
Cocaine	1.0	–	–	±	+				
		–	–	±	±	+			
		–	–	±	±	+			
Novocaine	0.5	–	–	±	±	±	±	+	
		–	–	–	±	±	±	±	+
		–	–	±	±	±	±	+	
Novocaine	1.0	–	–	±	±	+			
		–	–	±	+				
		–	–	±	±	+			
		–	–	±	±	+			
		–	–	±	±	+			
Apothesine	0.5	–	–	±	±	±	+		
		–	±	±	±	+			
		–	–	±	±	±	±	+	
		–	–	±	±	+			
		–	–	–	±	±	±	±	+
Apothesine	1.0	–	–	±	+				
		–	–	±	+				
		–	±	+					
		–	–	±	+				
		–	–	±	±	+			
KCl	0.5	–	–	–	–	±	±	±	+
	1.0	–	±	±	±	+			

TABLE II

TIME IN MINUTES REQUIRED FOR COMPLETE ANESTHESIA OF THE WHOLE LENGTH OF THE SCIATIC NERVE

	.05% SOLUTION	1% SOLUTION
Cocaine	12-25	10-12
Novocaine	20-25	10-12
Apothesine	15-25	10-12
Potassium Chloride	25	12

It was planned to use such dilutions only as would bring about complete anesthesia in five to ten minutes but the lower time limit was in no case sufficient with the dilutions used.

The irritation was produced from a three cell battery through a secondary with 5000 windings adjusted to a point where the current is just perceptible on the tongue.

The sciatic nerve of the frog is dissected, leaving a small piece of the bone

attached, for convenience in handling, and having the whole muscle below the knee skinned but otherwise intact.

After determining that its response to stimulation is good, the whole nerve-muscle preparation is immersed in the solution, testing frequently after five minutes to determine when anesthesia begins and its progress. It will be observed that no account is taken of certain features which have formed an important part of the reports of other investigators, namely, the response to varied degree of current, the response from application of stimulus to different portions of the nerve, the exact beginning of paralysis, its duration or the recovery. While these factors are not unimportant this series of tests was made primarily to compare the efficiency of several local anesthetics, and for this purpose, one end point may be considered as good as another, other things being equal. The end point chosen was therefore that dilution which would paralyze the motor nerve all the way to its disappearance into the tissue below the knee, in a period of approximately ten minutes. However, for comparison and as evidence of different degrees of anesthesia records of other times and of other dilutions are included.

In the table, — means practically no degree of anesthesia, ± means partial anesthesia in the sense of progress along the nerve, + means complete anesthesia except the nerve just at its disappearance into the tissue of the leg.

From Table I the efficiencies of the four anesthetics are apparently so nearly equal that for all practical purposes their values by this method may be taken as equal, as shown by Table II which summarizes the results.

Comparison of these results with those of Sollmann shows that there is absolute agreement in ratio so far as each of us carried our experiments but that the efficient concentrations used are somewhat different. This is probably due to the selection of different constants and not to errors on either side.

The added data on apothesine is valuable, since the virtual agreement on the others points to a probable agreement on this substance.

SURFACE ANESTHESIA

The method is that of Gradenwitz[5] who first applied it as a means of determining the relative values of local anesthetics. The brain, medulla and heart of the frog are removed and the blood washed out to prevent general absorption of the substance which is being tested. In applying this method, one leg, after removing excess moisture, is dipped into the diluted anesthetic for 1 minute, after which it is laid in a vessel containing cold water but with the legs not immersed and separated so that none of the anesthetic touches the control leg. At five minute intervals both feet are dipped into a weak solution of hydrochloric acid (about 1/5 per cent) and the behavior closely observed. When no anesthesia has taken place both legs are withdrawn with equal promptness while as anesthesia progresses the treated leg is more slowly withdrawn until on complete anesthesia it is not withdrawn at all while the control leg reacts as promptly as at first. After each stimulation both legs are dipped in water to remove any adhering acid.

The objection has been raised that there is no direct relationship between this method and clinical practice; on the other hand the frog's skin being al-

ways moist is in a sense comparable to the mucous membrane and, in this respect, is an experimental method for obtaining relative values for mucous membrane anesthesia. Besides, it is a method with a reaction susceptible of quite exact measurement and as such takes its place as a valuable pharmacologic assay method for establishing relative values. The values so obtained may not be capable of direct application as has been stated about other methods but without question, they are not to be ignored in assigning the real position of a local anesthetic.

Table III

SUBSTANCE	DILUTION %	TIME AND RESULT OF OBSERVATION 5	10	15	20	25	30	35	40	45
Cocaine	2	+	+	+	+					
	2	+	+	+	+			0		
	1	+	+	±±			0			
	1	+	±±	±±	±	±	±	±	0	
	½	±	±	±	±	±±±	0			
	½	±	±±±	±±±	±±	±±±	±±±	0		
	⅔	–	±	±	±±	±±±	±±±	±±±	±±±	0
Novocaine	2	–	±	±						
	2	–	±	±			0			
	2	–	±	±			0			
	3	–	±	+±	±±	+±	+±	+	0	
	3	–	–	–	±	±	±±	±±	+±	
	3	–	±	±±	+	0				
	3	–	±	±±	±±	+±+	0			
Apothesine	2%	0	±	±	±	+	0			
		–	±	±	–	0				
		±	±	±	±±	±±	±			
Apothesine	3	–	±	±±	±±	+±+	+	+	±±±	
	3	–	±	±±	±±	±±	+	0		
	3	±±	±	±±	±±	±±	+	+	0	
	3	–	±±±	±±±	±±±	0				
KCl	1	–	±	±	–	–	0			
	2	–	±	±	±	±	–	0		
	3	+	+	+	±±	±±	±±	±±	0	
	2½	±	±±	±	±±	±±	±±	0		

Summary of Table IV

SUBSTANCE	EFFECTIVE DILUTION	RATIO OF EFFECTIVENESS
Cocaine Hydrochloride	1 per cent	1
Novocaine	3 " "	⅓
Apothesine	3 " "	⅓
Potassium Chloride	3 " "	⅓

Table III shows the detailed results in which equally prompt withdrawal of the legs is represented by —, progressive anesthesia by ±, while complete anesthesia of the treated member only is represented by +. When neither leg will respond to stimulation this condition is represented by 0.

Comparing these relative efficiencies with those obtained by Sollmann it is seen that he found it necessary to use a solution of novocaine six times as strong as that of cocaine as against one three times as strong in Table III. Also that of KCl, the efficient strength was twelve times as great as for cocaine against three times in Table II.

INTRACUTANEOUS METHOD

This method has the distinct advantage of most nearly duplicating one of the important uses of a local anesthetic since it is carried out in a way almost identical with that in clinical practice. Particular care was taken in the tests tabulated below to prevent the unintentional prejudice which knowledge of what was injected might have.

The injections were made by a practicing physician into the forearms of the subjects, who were asked to respond only when pain was felt when a needle prick was made on the anesthetized area or the adjacent skin.

EXPERIMENTS ON FIRST SUBJECT (H. C. H.)

First Series

	AMOUNT	DILUTION	RESULT
Cocaine	0.25 c.c.	1-500	Complete
Novocaine	0.25 c.c.	1-200	Complete
Apothesine	0.25 c.c.	1-200	Complete
Phys. Salt Sol.	0.25 c.c.		No anesthesia

Anesthesia was so complete that no distinction could be drawn between the different injections. The second series was therefore made with the same ratio of strengths but each reduced to half that in the preceding series.

Second Series

	AMOUNT	DILUTION	RESULT
Cocaine	0.2 c.c.	1-1000	Complete
Novocaine	0.2 c.c.	1-400	"
Apothesine	0.2 c.c.	1-400	"

In this test while anesthesia was complete in every case it seemed more persistent in the area injected with apothesine and in the next series the strength of the latter only was changed.

Third Series

	AMOUNT	DILUTION	RESULT
Cocaine	0.2	1-1000	Complete
Novocaine	0.2	1-400	Complete
Apothesine	0.2	1-800	Complete

In this series the anesthesia was as nearly identical as impartial observation could recognize.

The experiments were continued the next day on the same subject.

In the data below an attempt is made to indicate the degree of anesthesia and its duration by the number of plus signs.

First Series

	AMOUNT	DILUTION	RESULT
Cocaine	0.2 c.c.	1-1000	++++
Novocaine	0.2	1-500	+++
Apothesine	0.2	1-1000	++++
	Second Series		
Cocaine	0.2	1-2000	++
Apothesine	0.2	1-2000	+
	Third Series		
Cocaine	0.2	1-2000	++
Apothesine	0.2	1-1500	++

The above injections were made with not to exceed a minute interval between those of a series.

The results of these tests are summarized in Table V.

TABLE V

SUBSTANCE	DILUTION	RATIO
Cocaine	1-2000	1
Novocaine	1-1000	½
Apothesine	1-1500	¾

Experiments on a second subject (M. W.) were carried out, the degree of anesthesia being indicated roughly by the number of plus signs.

EXPERIMENTS ON SECOND SUBJECT

First Series

	DILUTION	RESULT
Cocaine	1-2000	+++
Novocaine	1-1000	++
Apothesine	1-2000	+++
	Second Series	
Cocaine	1-3000	++
Novocaine	1-2000	+
Apothesine	1-3000	++
Novocaine	1-1000	++

These results may be summarized in Table VI.

TABLE VI (M. W.)

	DILUTION	RATIO
Cocaine	1-3000	1
Novocaine	1-1000	⅓
Apothesine	1-3000	1

On a third subject (W. E. K.) the results were as follows:

EXPERIMENTS ON THIRD SUBJECT

First Series

	DILUTION	RESULT
Cocaine	1-3000	+++
Novocaine	1-1800	++
Apothesine	1-3000	+++

Second Series

Cocaine	1-4000	++
Novocaine	1-2000	+
Apothesine	1-4000	++

TABLE VII (W. E. K.)

SUMMARY ON THIRD SUBJECT

SUBSTANCE	DILUTION	RATIO
Cocaine	1-4000	1
Novocaine	1-1800	less than ½
Apothesine	1-4000	1

EXPERIMENTS ON FOURTH SUBJECT (L. W. R.)

First Series

	DILUTION	RESULT
Cocaine	1-2000	+++
Novocaine	1-1000	++
Apothesine	1-2000	+++

Second Series

Cocaine	1-3000	++
Novocaine	1-1800	++
Apothesine	1-3000	+

Third Series

	DILUTION	RESULT
Cocaine	1-4000	+
Novocaine	1-1500	++
Apothesine	1-4000	+

Fourth Series

Cocaine	1-3000	++
Apothesine	1-3000	++

Summarizing these results the ratios are shown in Table IX.

TABLE VIII

SUMMARY OF AVERAGE RESULTS BY INTRACUTANEOUS ADMINISTRATION

SUBSTANCE	RATIO
Cocaine	1
Novocaine	$11\frac{1}{24}$
Apothesine	$15\frac{1}{16}$

TABLE IX (L. W. R.)

SUBSTANCE	DILUTION	RATIO
Cocaine	1-3000	1
Novocaine	1-1500	½
Apothesine	1-3000	1

The results of the intracutaneous administration of the three local anesthetics summarized above, carried out as they were on four different persons prove conclusively two points, (1) novocaine is about one-half as efficient as cocaine, (2) apothesine is practically equal to cocaine in anesthetic value. Sollmann's conclusions from his test by this method, namely, that novocaine is equal to cocaine, and apothesine one-eighth as efficient are evidently incorrect. It is impossible to explain this discrepancy. Novocaine anesthesia is

well known to be less permanent since most observers have noted quick recovery. This, however, was not the factor in these tests since the time of recovery was only incidental in importance as compared with the degree of anesthesia from the high dilutions.

In the introduction it was stated that since tests of local anesthetics by different methods do not show entire agreement, they can be taken as only suggesting and not demonstrating the clinical value. Viewed in another way, however, it may be said that these tests demonstrate comparative efficiencies in the particular method of applying the substance.

That both novocaine and apothesine are inferior to cocaine by surface application agrees with clinical evidence which has demonstrated cocaine to be exceptionally rapid in its absorption from mucous surfaces. Braun.[4] The comparative efficiencies of cocaine and novocaine by intracutaneous injection also duplicates the opinion generally held that the latter is less efficient. On this point, Braun[4] states: "Experience and experiments have, however, shown that by doubling the dose of novocaine so as to make it as effective as cocaine, and at the same time by adding certain substances which will be described in the next chapter (suprarenin) novocaine has become an ideal anesthetic for injection of tissues and has made cocaine unnecessary." It may be assumed therefore that this method correctly measures the efficiency of apothesine as well as those of cocaine and novocaine. Verification of the motor nerve method can not be cited at this time.

Based on the foregoing results it is evident that from every point of view apothesine is equal to or exceeds novocaine as a local anesthetic and in some respects is not less efficient than cocaine. We can therefore be assured of supplies of an efficient product, independent of German patents or controlled United States laboratories operating under license to German patentees.

The author's appreciation is extended to Dr. A. W. Lescohier, who carried out the intracutaneous tests and recorded his observations; also to three associates who by their courtesy made more data available.

TABLE IX

SUBSTANCE	METHOD	GRAPHIC ILLUSTRATION OF EFFICIENCIES	RATIO
COCAINE	Motor Nerve	═══════	1
	Surface	----------	1
	Intracutaneous	++++++++++++++++++++++++++++	1
NOVOCAINE	Motor Nerve	═══════	1
	Surface	----------	⅓
	Intracutaneous	++++++++++++	½
APOTHESINE	Motor Nerve	═══════	1
	Surface	----------	⅓
	Intracutaneous	++++++++++++++++++++++++++++	1

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[4]Idem: p. 122.
[5]Gradenwitz: Ber. klin. Wchnschr., 1899; xxxvi, 76.

LABORATORY METHODS

SIMPLIFIED GAS ANALYSIS

By J. J. R. Macleod, M.B., Toronto, Canada

NO. II. BURETTE WITHOUT STOPCOCKS FOR GAS ANALYSIS

FOR purposes of teaching, as well as for occasional use in clinical practice, the usual types of gas burette are unsuitable because of the care and attention that has to be given them in order to prevent "freezing" of the stopcocks. Other objections to stopcocks are that they are liable to leak unless well ground, and they add considerably to the cost of the apparatus. The increasing necessity of gas analysis in medical diagnosis and in research makes it important that simple and reliable apparatus be available.* Such an apparatus can be constructed by using screw clips in place of stopcocks, provided some means be taken to adjust the gas pressure in the burette after the screw clips have been tightened. This can be accomplished by the use of the "pressure adjuster" described below.

Another difficulty which the inexperienced constantly meet with in using gas burettes of the usual pattern (Haldane's) is in preventing the strong alkaline solution from running up the narrow tubing which connects the burette and absorption bulbs. This accident delays the analysis, since all traces of the alkali must be removed from the burette and mercury before proceeding with the analysis, and moreover the alkali, if not removed, eats its way around the stopcock, and causes etching of the glass and "freezing." In the following apparatus this danger is guarded against by inserting a small bulb on the connecting tubing. The adjustment of the mercury—very little of which is required—is simplified by using a screw clip and pinchcock on the tubing connected with the leveling burette.

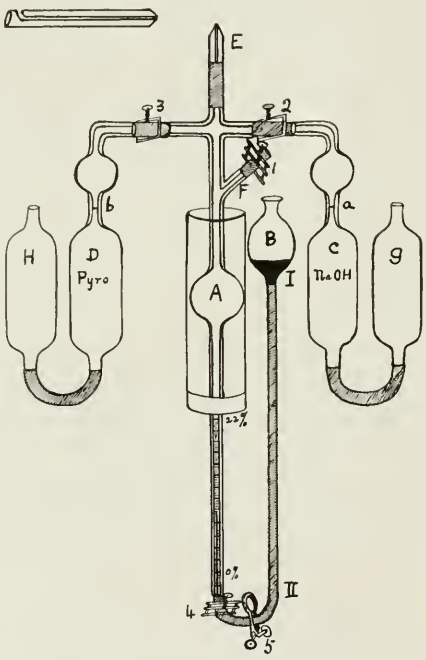
DESCRIPTION OF THE APPARATUS

The gas burette (*A*) is 10 c.c. capacity from the end of the oblique side tube (*F*) to the lowest graduation on the narrow portion. The uppermost graduation corresponds to 2.2 c.c. from the lowest, the distance between the two being divided into c.c. and 1/50th c.c. The bulb part of the stem to just above the 2.2 mark is surrounded by a water jacket. Above the side tube (*F*) the burette is continued into a narrow-bored tube (narrower than represented in the diagram), with two arms at right angles to each other. These are connected by thick-walled pure-gum tubing, with the absorption bulbs (*C* and *D*) containing re-

*It is not suggested that the apparatus herein described should be employed by those accustomed to the use of the standard burettes or where expense is no object.

spectively a 20 per cent solution of NaOH and a 60 per cent solution of KOH with 10 per cent pyrogallic acid dissolved in it.*

Each bulb is connected below by rubber tubing with the overflow bulbs (*G* and *H*). A small bulb (relatively smaller than represented in the diagram) is blown on the stem of each absorption bulb to serve as a trap preventing the solutions from passing over into the burette. The vertical tube above the cross tubes is closed by the *pressure adjuster*, which consists, as shown in the small side sketch in the diagram, of a glass rod beveled at one end and bored most of the way down the center. At a distance of about 3 mm. from where the beveled portion joins the tube a lateral hole is bored to meet the channel in the center. The adjuster is connected by pure-gum tubing with the central tube of the burette, the beveled end of the former being in contact with the end



of the latter. When the rubber tubing is pinched up opposite the side tube, the burette is brought into communication with the outside and the pressure in it remains undisturbed when the tubing is allowed to fall back into place.

The lower end of the burette is connected by thick-walled rubber tubing with the reservoir (*B*), and on this tubing are a pinchcock (*5*) and screw clip (*4*). About 15 c.c. of mercury suffices to fill the apparatus. The reservoir is hung by a loop of wire around the neck on hooks placed on a wooden upright stand, the higher one being in such a position (marked I†) that the mercury stands at the end of the side tube (*F*), and the lower one (marked II) so that it stands exactly at the mark 0% on the burette.

*NaOH may be substituted for KOH, but is not so satisfactory because of its viscosity. The best solution is made by dissolving pure NaOH (electrolytic, if possible) in an equal weight of water, diluting 10 c.c. of this solution with 4 c.c. water, and dissolving 10 gm. pyrogallic acid in the resulting mixture. Shipley: Jour. Am. Chem. Soc., 1916, xxxviii, 1687.

†The position I should be at a higher level than is shown in the figure.

TECHNIC OF THE ANALYSIS

The first step is to fill the tubing between the side tube (*F*) and the absorption bulbs with nitrogen. This is accomplished by taking a sample of air in the burette by opening screw clip 1, placing the mercury reservoir so that it stands opposite the lower end of the burette (at II), and with the screw clip (*4*) open, cautiously opening the pinchcock (*5*) so that air enters the burette. The screw clip (*2*) is then opened and the reservoir (*B*) raised to position I. By cautiously opening the pinchcock (*5*) the air is made to pass into *C*, and with *5* open the reservoir is raised and lowered several times so that all traces of CO_2 are removed from it by the alkaline solution, after which the reservoir is replaced in position II and the pinchcock, previously closed, opened until the NaOH stands at the mark (*a*) on the stem. Screw clip *2* is then closed, *3* opened, and the oxygen removed from the air by repetition of the same procedure. Screw clip *3* is then closed. This preliminary filling of the burette with nitrogen is unnecessary if a previous analysis has been made.

The sample of gas for analysis is now collected in an all-glass (Luer) syringe with the piston well lubricated with vaseline. With the screw clips (1) open, the burette is filled with mercury up to the end of the side tube (*F*), and the nozzle of the syringe is inserted in the rubber tubing of the side tube. While making this connection the piston of the syringe should be gently pressed so that no air may be allowed to become entrapped in the rubber tubing on *F*. To aspirate the sample into the burette the reservoir is placed in position II and the pinchcock *5* opened, gentle pressure being meanwhile maintained on the piston of the syringe. After the gas has been transferred, the mercury meniscus should stand about 1 mm. below the 0 graduation on the burette, this being accomplished by gentle pressure on the piston of the syringe. This leaves the gas in the burette under a slight positive pressure.

The pressure in the burette must now be made equal with that of the atmosphere. For this purpose the pinchcock (*5*) and all screw clips except 1 are opened, and the tubing on the adjuster (*E*) is pinched opposite the bevel. Being under a slight positive pressure, some of the gas in the burette escapes through the adjuster, and it is during this procedure that a slight error is incurred because some of the sample of gas mixes with the nitrogen above the side tube. The error thus incurred is, however, negligible for most purposes. The meniscus of mercury should now stand exactly at the 0% mark.

Screw clip 3 is now closed. This slightly compresses the gas in the burette and lowers the menisci at *a* and *b*, the new level at *a* being marked on the glass by a glass pencil. The reservoir (*B*) is slowly raised and lowered several times (with 4 and 5 open) so that the gas passes in and out of *C*, in which the CO_2 is absorbed. In doing this, care must be taken that the mercury does not rise above the level of *F*, and that the NaOH solution does not rise higher than the mark *a*. Four movements usually suffice to absorb all of the CO_2.

To determine the volume of the remaining gas, the pinchcock (*5*) is closed, the clip (*4*) half way screwed down, the reservoir placed in position II, and the pinchcock then cautiously opened until the NaOH solution is as nearly

as possible brought back to its original position at *a*. The fine adjustment of this level to the pencil mark is finally effected by means of screw clip *1*. The reading on the burette opposite which the mercury now stands gives in cubic centimeters the amount of CO_2 in 10 c.c. of gas. To make certain that all the CO_2 has been absorbed, the above procedure should be repeated.

To determine the oxygen, screw clip 2 is closed and 3 opened. The level of the meniscus of the pyrogallic acid solution is marked with a glass pencil at *b*. The gas is then moved in and out of D several times, until all the oxygen is absorbed as determined by no further shrinkage. This takes considerably longer than for CO_2. The final volume of gas as read on the burette, less the volume of CO_2, gives the oxygen.

After completion of the analysis the apparatus should be left filled with nitrogen and with the screw clips all closed. A short piece of rubber tubing should also be connected with the upper end of the reservoir (*H*) and closed by pinchcocks. This is to prevent undue oxidation of the pyrogallic solution.

As above remarked, a slight error is incurred in using the above apparatus during the adjustment of the pressures. With a little practice, however, this becomes very small. It is very important to make certain that all the rubber unions are perfectly tight, which is best insured by wiring the tubing.

The following analyses for CO_2 made by Mr. Shen will serve to illustrate the degree of accuracy of the method.

1. Mixture of nitrogen and CO_2 from stock bottle: CO_2, 1.78, 1.79, 1.81, 1.76; average, 1.785. Another mixture: 1.91, 1.99, 1.95, 1.95; average, 1.950.

2. Samples of alveolar air taken in all-glass syringe by using the Haldane tube:

a. Deep expiration after a normal inspiration: 6.03, 5.88, 6.04, 6.09, 5.96; average, 6.00.

b. Deep expiration after a deep inspiration: 5.42, 5.38, 5.33, 5.23, 5.54; average, 5.38.

3. Samples of air aspirated from the mouth after a deep expiration. This was done by placing a short piece of rubber tubing attached to an all-glass syringe at the back of the mouth, closing the lips around it after making a quick forced expiration, and quickly withdrawing the piston, the "dead space" of the tubing having been filled with alveolar air by a preliminary trial of the procedure.

a. Deep expiration after a normal inspiration: 5.76, 6.07, 6.09, 6.10; average, 6.00.

b. Deep expiration after a deep inspiration: 5.42, 5.31, 5.44; average, 5.39.

A CONTRIBUTION TO THE TECHNIC OF ARTIFICIAL RESPIRATION IN MAN*

By G. N. Stewart and J. M. Rogoff, Cleveland, Ohio

THERE is a pretty general agreement that in attempting resuscitation in apparent death by electric shock, drowning, asphyxiation from gases, etc., artificial respiration should be at once begun by a manual method, the best being the prone pressure method recommended by Schäfer. The advantage, in many cases, of supplementing this later on, especially where the artificial respiration must be kept up a long time, by some mechanical arrangement neither liable to get out of order nor likely to be dangerous in the hands of a novice, has been pointed out by a number of writers whose acquaintance with the subject entitles them to speak with authority, and especially by Meltzer. Schäfer,[1] too, has remarked that the method of Horvath (forcing air into a nostril, by a bellows, the mouth being shut) "might well be employed in certain cases," although it "would not be available in most instances of apparent death from drowning; but its efficiency should not be forgotten, especially since it appears to afford a means of forcing air into the alveoli in cases in which the more gentle current of air which is produced by movements of the ribs, fails to find a passage through the frothy mucus which may partially block the bronchi."

Meltzer[2] quoting largely from Keith[3] points out that inflation of the lungs by bellows was long the accepted method in resuscitation of the apparently drowned. It seems to have been discontinued on quite insufficient grounds. Anyone who has had experience of the routine methods of artificial respiration in animals in the laboratory, which can easily be carried on without any cutting operation by the use of a properly shaped mask or by laryngeal intubation,[4] is aware of their great superiority over manual methods for long-continued respiration.

Meltzer has described a simple arrangement[2] which he considers superior to any of the more elaborate and expensive devices put upon the market by commercial firms. The current of air, maintained by a foot bellows, is interrupted at the desired rate by a respiratory valve actuated by a lateral movement of the thumb. A rubber bag is interposed between the bellows and the valve. Meltzer discards the close-fitting mask on the ground that the danger of infected material being forced into the lungs is increased by its use. For the mask he substitutes a pharyngeal tube of appropriate shape and size, the air being thus delivered to the patient by "pharyngeal insufflation." Others have raised objections to the "close-fitting" mask, and some have included in their condemnation all mechanical devices, the use of which according to them occasions neglect of the manual methods and delay in starting artificial respiration while the apparatus is being procured.

We have examined two forms of apparatus, Meltzer's and the commercial

*From the H. K. Cushing Laboratory of Experimental Medicine, Western Reserve University.

apparatus known as the "lung motor." Meltzer has shown that efficient respiration is easily maintained with his arrangement; a curarized dog, for example, being kept alive indefinitely. Although it seemed sufficiently obvious that this must also be the case with a pump like the "lung motor," we thought it worth while to demonstrate the point. There is no difficulty in maintaining with it efficient respiration indefinitely in a curarized dog. Of course, the mask must be of appropriate shape to fit a dog. One of the metal cones used for giving ether was found to answer admirably. A piece of sheet rubber was tied over the wide end and a round hole cut in the rubber, through which the dog's snout was pushed. The narrow end was closed by a cork, a tube in which communicated with the respiration apparatus. The animal's tongue was drawn out under the rubber and secured. This device is a convenient one for giving artificial respiration to animals which are to be allowed to survive, in an experiment or operation in which it is needed. It is theoretically an objection to the "lung motor" that the expiration is accomplished by a suction action of the pump. With a small animal the sounds accompanying this suction, extending widely over the thorax and even the abdomen, although apparently generated at the larynx, are alarming, but it was not possible to demonstrate that any harm was being done, so far as could be seen from the blood pressure curve or at autopsy. With a large animal the suction sounds were much less obtrusive. At the same time Meltzer's objection that this suction in expiration is unnatural and unnecessary seems to us a valid one, and it certainly seems better to allow the expiration to take place by the elastic recoil when the inflation ceases.

The foot bellows, with a rubber bag interposed, as recommended by Meltzer, appears to be the simplest and most practical method of obtaining the necessary pressure for inspiration. However, while there is no doubt that in skilled hands the pharyngeal tube is safe and efficient, we prefer a mask, as being simpler to adjust and better for general use. We believe that the mask for ordinary use should not be fastened in any way but merely held by the operator on the patient's face. This permits its removal at any moment for cleansing or for clearing out the mouth, and its immediate readjustment. We have also substituted for Meltzer's respiratory valve the valve shown in Figs. 1 to 3 (two-thirds of the actual size). The valve, constructed of aluminum, consists of a tube *T* (Fig. 1), one end of which is attached to the mask and the other end to a rubber bag kept filled with air by a bellows. A plunger *P*, is pressed in by the thumb or by the palm of the hand at the rate of fifteen to twenty times a minute. It is convenient to hold the valve with the four fingers applied to the tube, the plunger passing between the middle and ring fingers. When it is pressed in air passes through a hole bored across the plunger, and traversing the tube inflates the lungs. The position of the plunger in inspiration is shown in Fig. 2. The spring *S* (Fig. 1) is compressed as it goes in, and returns the plunger by its recoil as soon as the pressure ceases, allowing air to escape from the lungs through a hole bored longitudinally from the lower end of the plunger and then radially so as to open at one side of it, as shown in Fig. 3. The plunger carries a pin (*p*) which engages in the slot (*s*) and can move freely down the slot when the plunger is pushed in but can not return beyond the top of the slot when it is released. This prevents the possibility

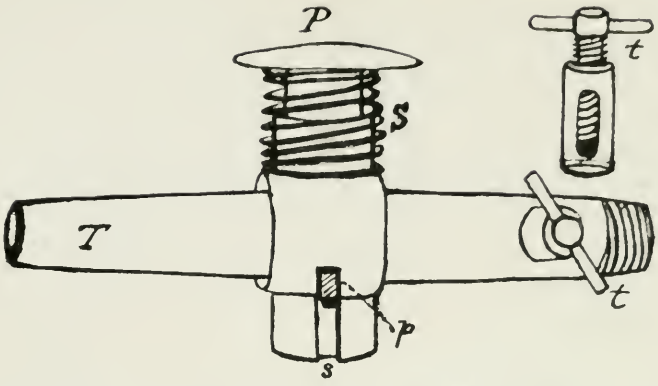


Fig. 1.—Respiration valve. *T*, tube through which air passes; *P*, plunger; *S*, spring; *p*, pin on plunger; *s*, slot in which *p* works; *t*, thumb-screw of safety opening shown separately in right-hand corner of figure.

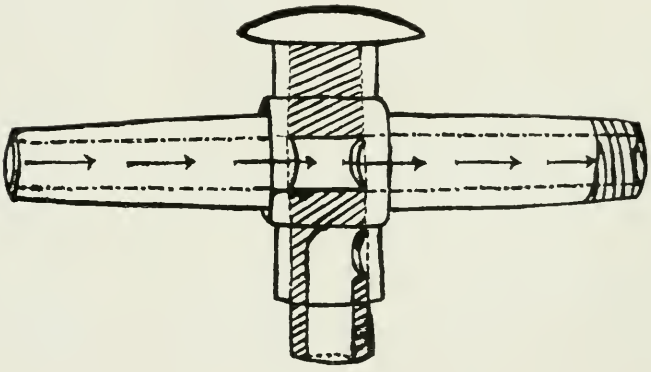


Fig. 2.—Section through respiratory valve showing position of plunger in inspiration.

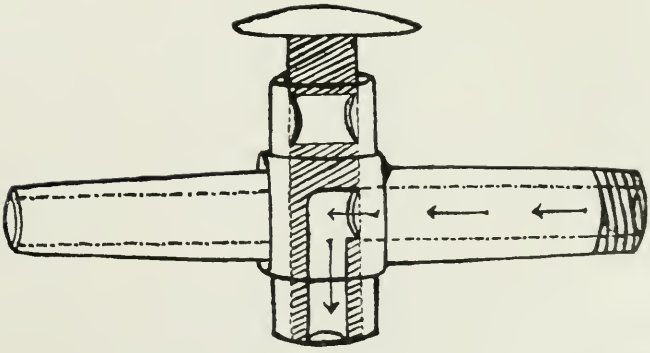


Fig. 3.—Section through respiratory valve showing position of plunger in expiration.

of the plunger coming out during the artificial respiration. A small thumb screw (*t*, Fig. 1) in a short side tube near the mask end of the tube *T* constitutes a safety arrangement to prevent the possibility of excessive pressure inside the mask. The side tube is slotted for the chief part of its length and by moving the screw, a greater or smaller permanent opening can be produced. The screw is arranged so that it is impossible to close the slot completely. The making of the safety arrangement and the valve in one piece we consider an improvement of some value, as it reduces the number of parts of the apparatus and, therefore, the time spent in connecting it up. A similar advantage is gained by the attachment of the valve directly to the mask. This also diminishes the dead space of the apparatus.

The valve can be taken apart in a moment for cleansing. To do this the plunger is removed by unscrewing the top. It is then easily pushed out of the tube *T*. The safety thumb screw (*t*) is also removable. The valve can be worked with great ease for long periods without fatigue. It can be operated by pressing with the first phalanx or the ball of the thumb or the palm of the hand. The valve is intended to be fastened to the mask so that one of the operator's hands suffices to work the valve and to hold the mask against the face, leaving the other free.

Since the operator may have to carry on the artificial respiration with the patient on the ground, an attachment has been fitted to the bellows which allows it to be worked conveniently by one forearm or one hand as well as by the foot. A wedge-shaped piece of wood is fastened to the top of the bellows so that its upper surface is nearly horizontal before compression. On this is hinged strongly a piece of wood about as long as the forearm. The hinge is situated at the edge of the bellows but the support projects two or three inches so as to increase the leverage. When the forearm is to be used, as is convenient when the operator is sitting down, the hinged piece is folded back over the bellows. The elbow is placed at the hinged end and the fingers project beyond and grasp the free end. Little effort is necessary in this way to keep the bellows going. When the hand is used, and it of course postpones fatigue in a long artificial respiration to vary the mode of compressing the bellows, the hinged piece is folded out so that it projects from the bellows and constitutes a lever.

As regards the question of what should be taught to the layman, our experience is in favor of teaching the immediate application of a manual method, followed by, or alternated with the employment of a simple mechanical device, when such is available. We do not believe that the average workman if taught to immediately begin with a manual method, the reason for this being sufficiently emphasized, and practiced in applying the mechanical device only later on when all is ready, will be at all likely to sit down and do nothing until an apparatus is procured.

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AN ADJUSTABLE TRACHEA CANNULA*

By John A. Higgins, Chicago, Ill.

If a laboratory worker, on animal experiments, were to visit other laboratories outside of the line in which he is directly concerned, the indications are that he would see various types of trachea cannulas in use by the various laboratory workers. Some laboratory workers prefer an ordinary piece of glass tubing for a trachea cannula. This piece of glass tubing is generally connected to a long piece of rubber tubing, which in turn is connected either directly or indirectly to an ether container. Where this method is used, the laboratory workers seem to consider as minor factors such points as the increased accumulation of carbon dioxide, which the lungs are constantly giving off with each exhaled breath, the increased amount of labor concerned in breathing through a long space of tubing, together with a constant loss of ether where air is inhaled and exhaled through the same ether container.

Another type of trachea cannula is the T-tube type. This type of cannula is best illustrated by Jackson.† Other types of trachea cannulas on the market are the ones manufactured by the Harvard Apparatus Company, Boston, Mass.; Charles Verdin, Paris, France; E. Zimmermann, Leipzig; etc.

A cannula which I have devised and which I wish here to describe can be used in the laboratory with attachments and for other uses. I have kept in mind the object of making a compact yet useful piece of apparatus and eliminating unnecessary dead space.

The cannula (Fig. 1) is made by taking a piece of ½ inch brass tubing 3½ inches long and making into an L-shaped piece by cutting or filing to the lower inside edge a V-shaped cut and using the uncut section of the V as a basis to make the L-bend upon.

On the front end of the L is soldered a short piece of 5/16 inch brass tubing (*A*). On the lower section of the L is soldered an outlet of ½ inch brass tubing ¾ inch long (*B*). On the upper surface of both the lower ½ inch pieces just described, and ¼ inch from the end of the tubes, are soldered small tits of a No. 12 or 14 gauge brass wire ⅛ inch high (*C*).

On the upper section of the L-piece is arranged a piece of telescope tubing, 9/16 inch by 1/32 inch wall brass tubing, and on the same order as the air regulator of a Bunsen burner with the exception that while a Bunsen burner has two air-hole regulators, the piece of tubing at this point is provided with one air-hole exhaust vent (*D*).

Just above the air regulator, or exhaust vent, is a valve chamber. This chamber is cup shaped, made from a piece of 11/16 inch tubing ½ inch high. It contains a ½ inch hole in the bottom and four smaller exhaust holes on the side. To the upper outside edge is fastened a ⅛ inch lip of sheet metal to

*From the Department of Physiology, University of Illinois School of Medicine.

†Jackson, D. E.: Experimental Pharmacology, 1917, St. Louis, C. V. Mosby Co., p. 87, Fig. 7.

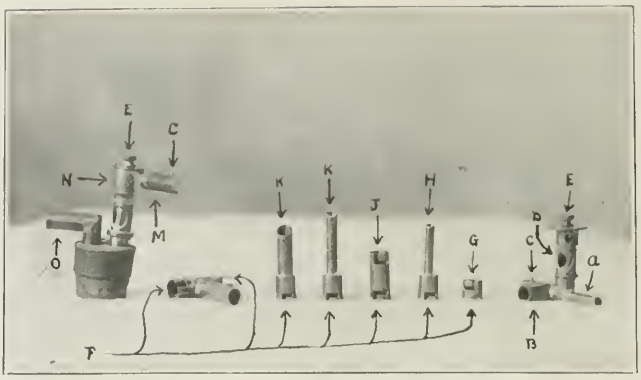

Fig. 1.—Showing individual parts of an adjustable trachea cannula. For description see text.

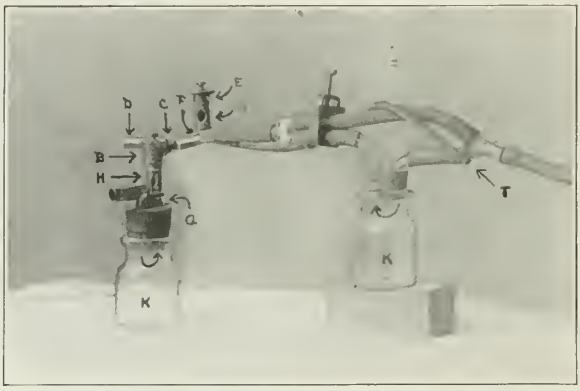

Fig. 2.—Adjustable cannula arranged for ordinary experiments and connected to artificial respiration tube. *K*, ether container and *T*, tube to tambour. For description see text.

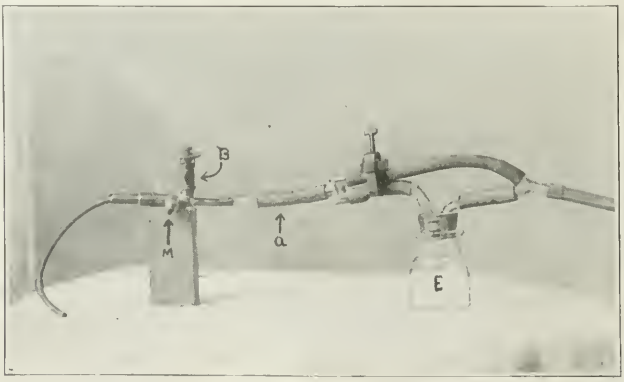

Fig. 3.—Adjustable cannula arranged for intratracheal insufflation experiments. *E*, ether container. For description see text.

which is fastened the lid by means of two screws coming through the lip and lid from the bottom, a No. 2 56 size screw being used.

Running down through the upper lid is a No. 8 32 set screw (*E*) which is used to lock the valve in the valve chamber when the valve is not in use. This set screw is of such a length and type that it snugly closes the valve and then automatically locks itself by a shoulder hitting the upper side of the lid. This also prevents further penetration or injury to the valve. The valve is a small disk of thin sheet copper about a 32-gauge coil spring wire. The coils of this spring wire should be about $\frac{1}{8}$ of an inch apart. The object of the coil spring is simply to keep the disk in an upright position and prevent its sticking to the lid, a result which might be caused by the exhaled vapors.

To the lower $\frac{1}{2}$ inch L-piece can be fastened various sized reduction tubes to accommodate different sized animal tracheas. These reduction tubes are made up by fastening any desired sized tubing, up to $\frac{1}{2}$ inch, into a piece of solid brass rod $\frac{1}{8}$ inch long by $\frac{1}{2}$ inch round. A piece of brass tubing $\frac{9}{16}$ by $\frac{1}{32}$ inch and $\frac{3}{4}$ inch long is then taken, and on one end is cut out a $\frac{1}{8}$ inch wide L-piece (*F*). This L-piece is simply cut out and used in the fashion of a lock with the small tit pieces previously described and shown at (*C*). The reduction tube is fitted snugly into a hole in the $\frac{1}{8}$ inch long by $\frac{1}{2}$ inch rod. The $\frac{9}{16}$ inch by $\frac{3}{4}$ inch tube is made to telescope the $\frac{1}{2}$ inch piece, with the cut end exposed, and the three pieces of metal are now soldered solid.

To the side outlet of the L, and in a similar manner as previously described, can be attached either a sealed piece of tubing (*G*); a straight tube connection (*J*); a T-tube connection (*I*); or a reduction tube (*K*). For ordinary blood pressure work, I would suggest using either a straight tube or a T-tube connection. Where artificial respiration may have to be resorted to, I would suggest the latter connection for use in the experiment.

At *M* (Fig. 1) is another piece of $\frac{1}{2}$ inch tubing which connects with the straight tube or T-tube. This short piece of tubing is soldered to the side of valve chamber (*N*), which chamber, although of a slightly different outside appearance from the valve chamber previously described, is in reality built on the same general principles—a disk, coil spring, and set screw to lock the valve.

To the lower end of this valve chamber is soldered a piece of $\frac{1}{2}$ inch tubing about 3 inches long. On the upper end of this tube is an air regulator similar to the one already described. The remainder of the $\frac{1}{2}$ inch tube is used to fasten into a cock stopper, which stopper in turn is fastened into the neck of a bottle or other ether container. At *O* (Fig. 1) is another small $\frac{1}{2}$ inch L-tube which penetrates through another section of the same cock stopper. This L-tube, however, can and should be omitted and was added solely to indicate an air passage to the ether container.

Where the T-tube is used as the connecting link between the cannula proper and the ether container section, the open end of the T-tube can be connected by tubing to the source of artificial respiration. I have devised a new type of adjustable screw clamp in connection with this cannula which I shall report in another article. The advantage gained, with the T-tube at this point, is to keep the artificial respiration tubes constantly connected, without

any fear of interfering with normal breathing, and to eliminate loss of time or trouble involved in making tube connections, etc., which trouble I have witnessed in animals at the last minute when respiratory movements were the main issue of revival.

The short piece of $\frac{5}{16}$ inch tubing, on the front end of the cannula, can be used with a tambour to record respiratory changes in the air system after the apparatus is connected and regulated for an experiment. This method of recording respiration will eliminate other simple methods; i. e., the stethograph drum method, the thistle tube, membrane and cock method, etc. Where the two last-mentioned methods of recording respiration are concerned, it must be considered that respiratory movements have a tendency to shift from the thoracic to the abdominal region or vice versa.

For ordinary experiments the apparatus ready for use will appear as illustrated in Fig. 2. On inspiration the air and ether vapors pass respectively through tube *A*, past the valve in valve chamber *B*, through tubes *C* and *D* and into the lungs, the valve in valve chamber *E* locking itself on inspiration. On expiration the valve in valve chamber *B* locks itself and forces the expired air through tubes *D* and *F* past the valve in valve chamber *E* and to the outside air. If the ether vapors, on inspiration, are too condensed, the anesthetist will be able to reduce such density by regulating the air inlet at *H*.

Where artificial respiration is desired, open air outlet at *G* (Fig. 2), lock valve in valve chamber E with the set screw and then gradually close the air outlet *G* until the desired flow of air is present. In cases where the artificial respiration is accidentally turned on into the system, previous to opening air outlet *G*, the valve in valve chamber *E*, if not locked, will act as a safety valve for any excess pressure in the lungs.

Where an intratracheal insufflation experiment is to be carried out, this apparatus can be so adjusted as illustrated in Fig. 3. This arrangement may be had by using the trachea insertion section as usual, connected with the cannula proper section, to the side outlet of which has been added reduction tube *H* (Fig. 1). To operate, insert cannula into the trachea in the usual manner. Next insert a thin-walled rubber catheter or a piece of $\frac{1}{4}$ inch black gum rubber tubing that will fit snugly into the $\frac{5}{16}$ inch tubing on the front end of the cannula. One end of this tubing should extend about 6 or 7 inches down the trachea of an average sized animal (dog). The other end of the tube should be connected to a reducing tube that will connect onto the air and ether vapor tube outlet. To reduction tube *H* (Fig. 3) is connected, by means of a rubber tube, a manometer to gauge the pressure used to inflate the lungs. With the air and ether vapors entering the lungs through tube *A* and with the valve in the valve chamber locked, it will then be only a matter of judgment to regulate outlet *B* and gauge the pressure desired to proceed with the remainder of the experiment.

A NEW TYPE OF ADJUSTABLE SCREW CLAMP*

By John A. Higgins, Chicago, Ill.

IN a previous article[1] I referred to a new type of adjustable screw clamp. This type of adjustable screw clamp was devised with the object of giving the anesthetist, and in certain animal experiments, a more perfect control of the air and ether vapors employed. Where the thoracic cavity has been exposed for work on the heart, lungs or other thoracic cavity structures or where intratracheal insufflation experiments are being carried out on the mammalian animal, it seems a customary procedure to control such animals with artificial respiration and ether.

The type of adjustable screw clamp heretofore employed in controlling air and ether vapor during an experiment, as previously mentioned, is best illustrated by Jackson.[2] With this older type of screw clamp the following few points are involved; that each tube requires an individual screw clamp; that it involves two separate operations to clamp down on one tube, while you release the pressure on the second tube; that there is more or less danger of unintentionally clamping down on one of the tubes before releasing the pressure from the second tube, etc.

Such points, as just mentioned, have been eliminated in this new type of screw clamp. The new type of screw clamp can be utilized on single tubes, and in the same way as the older type, with the added advantages. Each screw clamp can control two tubes in a single air and ether vapor system. The clamp is foolproof, and one can not close one tube without, at the same time, automatically releasing the pressure from a second tube, thus eliminating any danger of resistance in the artificial respiration system. Also the two, air and ether vapor, tubes involved can be regulated in one operation of adjustment.

This new type of screw clamp which I shall describe, and which is illustrated in Fig. 1, was made up from scrap pieces of copper rod taken from worn-out zinc battery plates. Since one can dispense with soldering joints in this new type of clamp I might suggest the use of a cheaper metal if available in the construction of other clamps of this type. The dimensions, as will be described, in connection with this screw clamp, were figured out to accommodate the use of one-half inch red antimony or white gum heavy walled tubing which in my opinion seems to be the most suitable variety of tubing for artificial work.

The clamp is made by taking a piece of $\frac{1}{8} \times \frac{3}{8}$ inch rod and bending in the vise a four-sided piece, making the bends on the larger flat surface, whose inside dimensions measure $\frac{7}{8}$ inch by one inch. The ends can then be fastened solid with No. 2 56 or smaller size screws. Care must here be taken to thread both ends and file the excess end of the screw away.

A U-piece is made up with the same size material, which piece should fit with slight play around the two long sides and one short of the four-sided piece previously described. The next step is to file down about $\frac{1}{32}$ of an inch from the $\frac{1}{8}$ inch surface of the four-sided piece or enough to allow a little play between the inside surfaces of two horizontal bars extended across the open, narrow and side ends of the U-piece. Now drill a No. 30 gauge hole in the

*From the Department of Physiology, University of Illinois School of Medicine.

[1]Higgins, John A.: This Journal, page 77.

[2]Jackson, D. E.: Experimental Pharmacology, St. Louis, 1917, C. V. Mosby Co., p. 111.

middle of one of the short, flat surfaces of the four-sided piece and thread this hole with a No. 8/32 tap.

Two pieces of the rod about ¾ inches long are then taken. In the middle of one and on the flat surface is drilled a hole that will permit a No. 8/32 screw to slip through easily. The hole is then countersunk and in such a fashion as to permit a small burr on the end of a No. 8/32 screw to slip around easily, but not so as to pull away. The countersunk surface of this piece is set against the flat surface of the yet undrilled short piece. Both pieces should be held firmly together and a No. 49 gauge hole drilled through both pieces, going through the flat surfaces close to the ends, and finally threaded with a No. 2/56 tap.

A No. 8/32 screw of about 1⅜ inches long, having a suitable head to work with the fingers, is taken and screwed from the outside into the 8/32 gauge

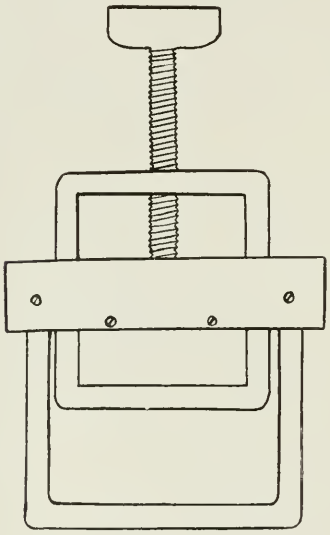

Fig. 1.—Pen and ink drawing of new type of adjustable screw clamp.

Fig. 2.—Showing new type of adjustable screw clamp in position on air and ether vapor (artificial respiration) tubes. For description see text.

threaded hole as previously made on the four-sided piece. Now place the short countersunk piece on the threaded end of the 8/32 screw, with the countersunk surface facing the opposite side of the 8/32 threaded section. A burr is then riveted to the threaded end of the 8/32 screw and the other short flat piece is fastened with 2/56 screws to the countersunk surface of the former mentioned countersunk piece. File away the protruding ends of the 2/56 size screws at this point.

Two horizontal bars, or a strap-like piece that will extend around the ends of the U-piece are now fastened evenly to the loosely fitted block and at the end of the 8/32 screw and fastened with 2/56 size screws. The U-piece is lastly slipped between the horizontal bars and fastened with screws of a 2/56 size. It is now a matter of judgment on leaving the screw heads, just set in, intact or filed away to come flat with the other metal surfaces. I have in my case taken the latter view. Fig. 2 will indicate the appearance as set on two tubes ready for service.

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EDITORIALS

The Bacteriology of Influenza

IN 1892 Doctor R. Pfeiffer announced his discovery of a bacillus which he believed to be the causative agent in epidemic influenza, and this claim seems to have met with ready and general acceptance. Pfeiffer examined sputum brought up from the bronchi. This was spread upon sterile glass plates, and the loop was taken from the purely purulent portion. The best preparations were made by staining with a dilute carbol fuchsin. It was found that the stain penetrates slowly, and the cover-glasses were allowed to float for from five to ten minutes in the solution. Pfeiffer made the following statement:

"In preparations of influenza sputum made under the above described precautions, we found in all recent and complicated cases a single, well-characterized species of bacillus in almost absolutely pure cultures, and always in surprising numbers. The bacilli are situated mostly in the form of nests and swarms in the mucous ground substance of the sputum. They are found also in greater or smaller number in the protoplasm of the pus cells where they are grouped around the nucleus without ever penetrating into the nuclear substance.

The influenza bacilli have not quite the transverse diameter of the bacilli of mouse septicemia. Their length, as a rule, is only two or three times their width, though occasionally we discover in the sputum, and sometimes in pure cultures, longer organisms that are to be regarded as filaments. In older pure cultures of from three to four days' duration, very long filaments may occur, but these are abnormal forms, the first signs of beginning involution. The ends of the influenza bacilli are rounded. Very often we found two particularly short bacilli in close apposition. These are forms of division that are apt to be interpreted as diplococci, and undoubtedly have been mistaken for them. The bacilli have no capsules and are nonmotile. They are gram negative, and in faintly stained specimens it is sometimes noticed that the poles are more deeply colored than the middle portion."

Pfeiffer was not able to grow these organisms upon gelatin or agar plates either aerobically or anaerobically, but he did grow them upon media containing blood, and ascertained that hemoglobin is the blood constituent essential to their growth.

Oxyhemoglobin is not essential, and boiling does not lessen the efficiency of the hemoglobin in the culture medium. On blood agar the colonies are minute droplets and when crowded can be seen only with the aid of a lens, but in sparse growths they may be seen by the unaided eye. The colonies have a glassy transparency and under the microscope appear to be without structure. The bacilli are strictly aerobic, and grow quite abundantly in bouillon containing hemoglobin. They do not multiply below 30° or above 43°. In drinking water they soon die, and they are very sensitive to drying.

From his experiments Pfeiffer came to the conclusion:

1. Any development outside the normal body, in the ground or in water is impossible.

2. The spread of the disease through dry sputum can occur only to a limited extent.

3. The contagion, as a rule, is conveyed by the recent, still moist culture from the nasal and bronchial mucous membrane of influenza patients.

4. Kitasato showed that pure cultures may be obtained directly from the sputum. The patient coughs the bronchial sputum into a double sterile dish. The sputum is thoroughly dissected with sterile needles, and during this process of disintegration it is carried through ten successive washings with sterile water. A bit of the washed sputum is examined microscopically and another portion is inoculated on the blood agar.

In uncomplicated influenza Pfeiffer found the bacilli in all cases in pure cultures in the bronchial sputum. When the influenza was engrafted on an existing bronchial affection, or when the influenza was complicated with bronchitis or pneumonia, other organisms were, of course, found in the bronchial sputum. Pfeiffer did not find the organism in the blood. The bacilli may persist in the sputum for months after recovery, and thus the individual may become a chronic carrier and distributor.

Pfeiffer's attempts to transmit the disease to mice, rats, rabbits, guinea pigs, swine, dogs and cats were wholly without result. His experiments with monkeys are worthy of recall at this time. Into the trachea of one of these ani-

mals he injected a flake of sputum the size of a pinhead, which had been found to be a pure culture, mixed in 1 c.c. of bouillon. The animal died after indefinite symptoms, and postmortem showed an abscess the size of a walnut at the site of inoculation. The pus of this abscess showed a few intact influenza bacilli and no other bacteria. Three monkeys had similar injections into the lungs through the thoracic walls. Some elevation of temperature took place after from twenty to thirty hours. The fever was remittent and transient. The animals coughed, but showed no typical influenza. Two weeks later they were reinoculated and developed milder symptoms. One was inoculated in the nose and showed a slight fever. Still another received an injection in the trachea and developed a temperature of 39.2° the same day. The next day the temperature began to fall and death resulted within forty-eight hours after inoculation, the temperature reaching 32.2°. This was not an infection, but an intoxication.

Rabbits died after a few hours from intravenous injection of the bacilli, but this results from similar treatment with the cellular substance of bacteria, known not to be pathogenic. Kruse made further animal experiments with the same lack of success. Up to the present time all attempts to induce influenza or any other infection in the lower animals with this organism have failed. The cellular substance contains a poison, but so do all proteins. We are compelled to conclude that it has not been proved that the Pfeiffer bacillus is or carries the virus of the disease we know as influenza. It may be a frequent, possibly a constant, accompaniment of the disease, but this does not prove that it is the cause.

—*V. C. V.*

Influenza Epidemic

THE following letter was sent out under date of October 16, 1918, by the Volunteer Medical Service Corps, Council of National Defense, to members of state executive committees and county representatives of the Volunteer Medical Service Corps:

"1. In view of the present serious epidemic which is sweeping over the country, the Volunteer Medical Service Corps earnestly invites your attention to the following important action:

"Urge upon the members of the Volunteer Medical Service Corps that they instruct families under their care to guard against the epidemic by:

"Thorough cleanliness of houses, premises, clothing, utensils, and personal cleanliness.

"Avoid stirring up dust.

"Wash; scrub; flush; sprinkle; and use soap and water thoroughly.

"Gargle and spray the nose and throat with an alkaline antiseptic fluid frequently.

"Cooperate at once to the fullest extent with the Local, State, and National Boards of Health. Urge and cooperate in preparing towns and cities for the epidemic by establishing emergency hospitals in suitable buildings, by district-

ing communities, and apportioning or dividing medical forces comprising men and women physicians and nurses so that no portion of the community is without medical care.

"Circulate as thoroughly as possible and explain to the public the warning and directions printed by the United States Public Health Service and by local health authorities.

"Urge the importance of fresh air and the avoidance of chill and overheat.

"In fighting the epidemic give no medicine and use no treatment which may depress the vital forces, especially the heart of the patient.

"2. The Army and Navy are fighting and conquering Germans. We must fight and conquer germs without taking anything away from the Army and Navy. Don't ask the Army and Navy for medical and surgical supplies. Use simple utensils for sterilizing; the simplest kinds of beds and bedding; make your own masks and dressings, and fight for yourselves.

"3. While the epidemic is on, do no surgical operations unless absolutely necessary to save life.

"4. In every way in your power urge the members of the Volunteer Medical Service Corps to cooperate to the fullest extent with the United States Public Health Service and with State and Local Health Authorities.

(Signed) EDWARD P. DAVIS,
President, Volunteer Medical Service Corps.

ERRATUM

In the article entitled "The Treatment of Dichlorethylsulphide ('Mustard Gas') Injuries," by Aldred S. Warthin, Ph.D., M.D.; C. V. Weller, M.S., M.D.; Capt. Lester Roos, M.D., and G. R. Herrmann, M.S., M.D., in the October, 1918, issue of the JOURNAL, page 848, the thirteenth line should read "use of .5 per cent solution" instead of "5 per cent solution."

The Journal of Laboratory and Clinical Medicine

VOL. IV. ST. LOUIS, DECEMBER, 1918 NO. 3

ORIGINAL ARTICLES

REPORT OF EPIDEMIC OF "SPANISH INFLUENZA" WHICH OCCURRED AT CAMP A. A. HUMPHREYS, VA., DURING SEPTEMBER AND OCTOBER, 1918*

BY I. W. BREWER, M.D., (GENEVA, N. Y.)

Lieutenant-Colonel, M. C., N. A., (Camp Surgeon, Camp A. A. Humphreys, Va.)

INTRODUCTORY

THE great pandemic of "influenza" invaded Camp A. A. Humphreys, Virginia, during the second and third weeks of September and continued until the third week in October, covering a period altogether of about five weeks. The morbidity and mortality experience for this period may be summed up briefly in the following figures:

Average strength of camp,	26,600
Number cases influenza,	4,237
Number cases pneumonia,	1,171
Number deaths from pneumonia and influenza,	413

On the basis of the above figures we may derive the following pertinent facts:

16% of camp had influenza.
28% of influenza cases had pneumonia.
10% of influenza cases died.
35% of pneumonia cases died.

This epidemic was therefore responsible for the death of 1.6 per cent of the population of this camp.

*Published by permission of the Surgeon-General's Office, Washington, D. C.

During the summer months there had been an occasional case diagnosed by regimental surgeons as "influenza." Probably some of these were severe "colds" and possibly some authentic cases of "influenza." These cases occurred as follows: Between July 1 and September 12 only two white organizations had any cases of "influenza." The 5th Regiment shows a record of 17 cases prior to September 12. There were 15 cases in this regiment during the month of August. The regimental surgeon, however, is of the opinion that most of these cases were colds, as none of them had a fever and the record shows they were only off duty for one day.

The 3rd Regiment reported one case of "influenza" on August 18. There were scattered cases among the colored organizations between September 1 and 11. The interval between these cases and what may be considered the new cases of the epidemic seem to preclude there being any connection between them, unless this disease, like others, is kept alive by carriers. Table I gives the data regarding "influenza" cases in the several organizations between September 1 and 12. So small a number of cases as these occurring at that time of the year in a command of the strength of Camp Humphreys should not have excited comment. However, between September 13 and 18, 134 cases were reported.

TABLE I

INCIDENCE OF NEW CASES OF "INFLUENZA" IN CAMP PRIOR TO EPIDEMIC
SEPTEMBER 1 TO 12, 1918

SEPTEMBER	1	2	3	4	5	6	7	8	9	10	11	12
ORGANIZATION												
3rd E. T. R.				1							1	1
5th E. T. R.												1
Casual Det.	2											
540th Ser. Bn.			1									
541st Ser. Bn.			1									
542nd Ser. Bn.	2											
543rd Ser. Bn.								1				
546th Ser. Bn.											1	2
547th Ser. Bn.										1		

It may be assumed that the epidemic began on September 13 and ended October 18. The early cases were practically confined to the 3rd Regiment, but as soon as these cases were known, all medical officers were notified of the impending epidemic and directed to take special precautions in diagnosing the cases and to take special steps in order to prevent the spread of the disease.

MEASURES USED TO CONTROL THE EPIDEMIC

The first measures taken to prevent the spread of the disease consisted of a circular addressed to all regimental and battalion surgeons, calling attention to the presence of the disease and calling for special reports each morning as to the number of cases. This was on September 18. On this day also, a popular article was displayed in the camp newspaper, telling what influenza is, its mode of transmission, and the means of prevention. (See Appendix A.)

On September 18 also, the Commanding General issued a memorandum calling attention to the seriousness of respiratory disease in the American Army. He ordered that beds be screened from each other by shelter halfs of tents. This memo also included a time schedule for lectures on respiratory disease, to be attended by each organization in camp. (See Appendix B.)

The lectures mentioned in this memo were given by the Camp Surgeon, and all organizations, except the colored battalions, the Officers Training School and the 3rd Regiment were visited. In these organizations the regimental surgeons were requested to make the necessary announcements.

On September 27, the Commanding General issued a memo advising the organization commanders to send men with colds to regimental surgeons for examination. (See Appendix C.)

On September 30, after consultation with the Surgeon-General's Office, the Camp Surgeon addressed a memo to regimental and battalion surgeons and surgeons of the Base Hospital, requiring that 100 square feet of floor space be provided for each patient, and that all men with colds should report twice a day for proper nose treatment. (See Appendix D.)

On the above date, the Commanding General issued a memo directing organizations to secure sheeting from the Quartermaster to be used as screens between beds. (See Appendix E.)

On October 3, the Commanding Officer issued a general order dealing specifically with crowding and living conditions in quarters, the fly question and the washing of mess kits. (See Appendix F.)

On October 3, an inspection of the camp was made by Colonel Chamberlain of the Surgeon General's Office. The Camp Surgeon has since that time received an unofficial report from the Surgeon-General's Office stating that the report made to the Surgeon General as a result of this inspection was highly satisfactory as to the methods adopted at Camp Humphreys for the handling of the epidemic. The following day, October 4, as the result of Col. Chamberlain's visit, the Camp Surgeon issued a circular addressed to medical officers, giving detailed information on the handling and care of the sick and convalescents, and on the care of quarters. (See Appendix G.)

On October 8, the Commanding General issued a memo limiting the crowding in tents and barracks and specifying certain measures to be taken to secure adequate ventilation, cleanliness, and freedom from flies in barracks. Further attention was drawn to laxity in cleansing dishes. Officers were warned to eliminate coughers at mess and in the Y. M. C. A. gatherings. Crowding in the Y. M. C. A. hall was also dealt with. Organization commanders were told to keep men out of doors as much as possible, to avoid giving them fatiguing exercise and to have them bathe at least twice a week. Further attention was called to the detection and examination and isolation of those with incipient colds. Mention was made of the antispitting rule. (See Appendix H.)

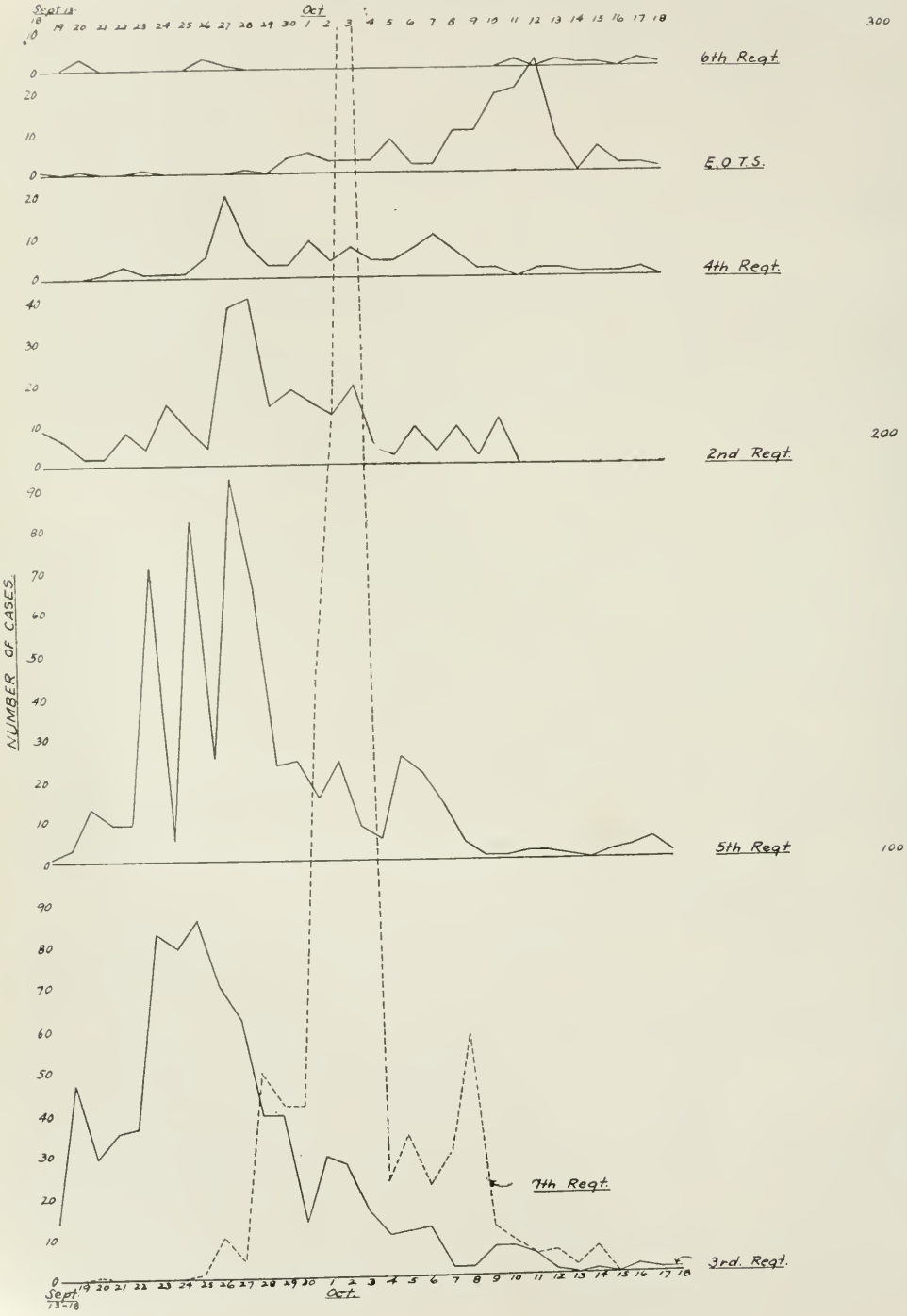
At no time during the epidemic was the camp under quarantine, and at no time were the men restricted in regard to their amusements. Although the Y. M. C. A. voluntarily omitted their usual entertainment features, the men

CHART 1.

INFLUENZA

Daily Record of New Cases in Various Regiments
During Course of Epidemic, Sept 13th-Oct 18th, 1918

CAMP A A HUMPHREYS, VA



were allowed to visit these buildings and the performances in the open-air theatre were continued throughout the epidemic.

During the first few days of the epidemic the Camp Surgeon visited the open-air theatre and various Y. M. C. A., Knights of Columbus, and similar buildings, and cautioned the men regarding spitting, explaining to them the importance of properly covering their faces while coughing or sneezing, and informing them as to the seriousness of the epidemic. It is believed these talks had a marked effect on the enlisted men.

At the beginning of the epidemic, verbal orders were given for the transfer of all influenza cases to the Base Hospital. As the epidemic progressed, and the cases became too numerous to be handled at the Base Hospital, it was necessary to open temporary hospitals in other parts of the camp. This was first done in connection with the 3rd Regimental Infirmary.

On October 4, Section J of the 3rd Regimental area was turned over to the Medical Department, in which a 500 bed hospital was established. This hospital annex was filled at once. It was evacuated October 27. Major Roscoe C. Hubbard, M.C., was in charge of the hospital annex, under the Commanding Officer of the Base Hospital.

PROGRESS OF EPIDEMIC

The epidemic lasted about five weeks and is summarized in Table II, which shows the number of cases developing each week during the epidemic and the percentage of the total. It will be seen from this table that the epidemic reached its maximum about the week ending October 4, when 52 per cent of the cases occurred. In all there were 4,237 cases up to, and including, October 18.

TABLE II

WEEKLY INCIDENCE OF NEW "INFLUENZA" CASES DURING THE FIVE WEEKS OF THE EPIDEMIC PERIOD OF SEPT. 13 TO OCT. 18, 1918

WEEK OF	NUMBER OF NEW CASES	PER CENT OF TOTAL CASES
Sept. 13-18	134	3.2%
Sept. 21-27	964	22.6
Sept. 28-Oct. 4	2208	52.2
Oct. 5-11	780	18.4
Oct. 12-18	151	3.6
Total	4237	100.

Table III shows the incidence of cases by days from September 13 to October 18. It also separates the cases according to color.

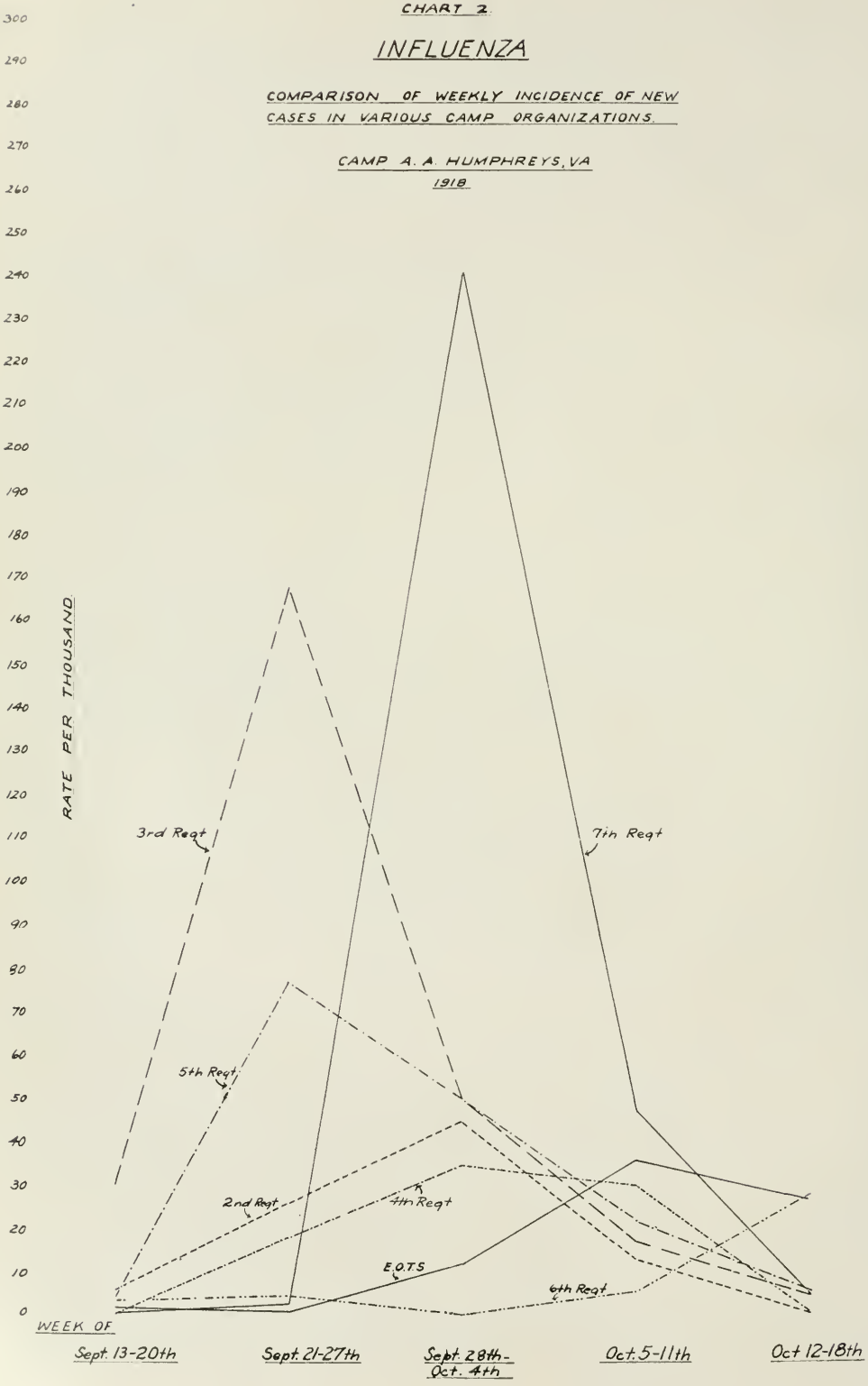
The data in Table III are shown in Chart 1. This is interesting in that it shows the waves of the epidemic in the different regiments. It also graphically shows the intensity of the epidemic in each organization. The lines appearing on this chart are the new cases each day in the various organizations. There are some fluctuations in the line, especially in the 5th Regiment, which are not readily understood, but are probably caused by clerical errors in reporting cases on the various days. From this chart it will be seen that the 3rd and 5th Regiments were infected almost simultaneously, and that the 3rd Regiment reached

CHART 2.

INFLUENZA

COMPARISON OF WEEKLY INCIDENCE OF NEW CASES IN VARIOUS CAMP ORGANIZATIONS.

CAMP A. A. HUMPHREYS, VA
1918



its maximum on the 25th day of September, while the 5th Regiment did not reach its maximum until two days later. These maxima are almost practically coincident with the maxima in the 2nd and 4th Regiments. The 7th Regiment was affected somewhat later than the others, but suffered more severely. The maximum in that regiment was reached by October 3, and there was a secondary maximum about October 8. This may possibly be explained by the fact that

TABLE III

RECORD OF NEW CASES OF INFLUENZA, BY DAYS. WHITE AND COLORED SOLDIERS
PERIOD—SEPT. 13 TO OCT. 18, 1918

DATE	WHITE	COLORED	TOTAL
Sept. 13-18	25	4	29
19	56	0	56
20	49	0	49
TOTAL FOR WEEK	130	4	134
Sept. 21	47	1	48
22	56	0	56
23	160	3	163
24	100	6	106
25	179	8	187
26	117	19	136
27	239	29	268
TOTAL FOR WEEK	898	66	964
Sept. 28	206	35	241
29	125	26	151
30	148	29	177
Oct. 1	354	28	382
2	308	45	353
3	725	46	771
4	112	21	133
TOTAL FOR WEEK	1978	230	2208
Oct. 5	144	46	190
6	104	20	124
7	107	14	121
8	115	22	137
9	57	8	65
10	60	23	83
11	45	15	60
TOTAL FOR WEEK	732	148	780
Oct. 12	47	7	54
13	20	6	26
14	14	0	14
15	12	2	14
16	13	2	15
17	15	0	15
18	12	1	13
TOTAL FOR WEEK	133	18	151

between October 4 and 8 there were several regimental surgeons taken sick and the record may have become somewhat confused. This chart also shows the low incidence of the disease in the 4th Regiment, the Engineer Officers' Training School, and the 6th Regiment. This matter will be discussed more fully under another heading. Here it may be said that these regiments were provided with cubicles some weeks before the epidemic appeared and there was less crowding than in the other regiments, which is shown on another chart.

From the 13th to the 18th of September a total of 29 cases was reported.

CAMP A.A.HUMPHREYS, VA.
Scale - 1000 ft = 1 inch.
Drawn by H W H
Oct 1918.
ACCOTINK BAY
GUNSTON COVE
POTOMAC RIVER
Dogue Cr.
BASE HOSPITAL
BELVOIR
DEVELOPMENT BATTALION 28.9
CASUAL DETACHMENT AND SERVICE BATTALIONS
COLORED RATE 76.
LAYOUT OF CAMP ORGANIZATIONS AND INFLUENZA RATE PER 1000 DURING EPIDEMIC SEPT.13th–OCT.18th, 1918.

half of these occurring in the 3rd Regiment. Most of these cases were reported on September 17 and 18. On September 19 only three organizations in the camp reported new cases, the total being 56, 46 of them being in the 3rd Regiment. On September 20 there was a total of 49 cases in seven organizations, 59 per cent being in the 3rd Regiment and 27 per cent in the 5th Regiment. In the second week of the epidemic the 3rd and 5th Regiments furnished about 80 per cent of the cases. During that week the epidemic spread to other organizations and increased very much. The third week of the epidemic marks the climax in most of the organizations, but the epidemic had already begun to decline in the 3rd and 5th Regiments.

Table III shows the incidence of cases by days from September 13 to October 18. It also separates the cases according to color.

CHART 3.

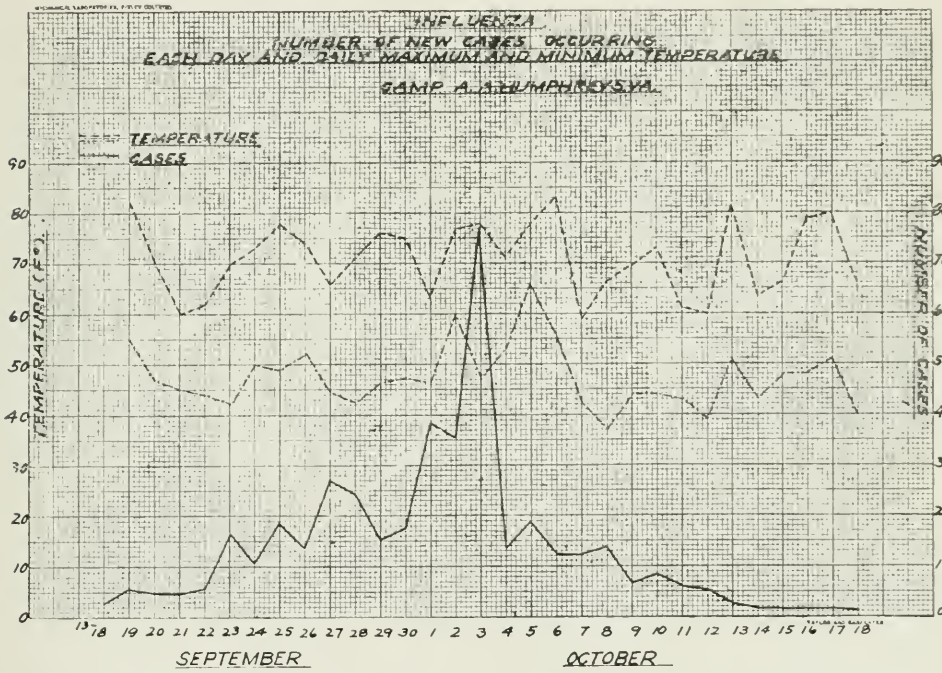


Chart 2 shows the weekly incidence of new cases in the white organizations, and is based upon rates per thousand as for the average strength of the command for these weeks. It shows that during the third week there was a general drop in all organizations except the 6th Regiment and the Engineer Officers' Training School. These two organizations suffered less severely from the epidemic than did the others and were somewhat later in infection. At the end of the 5th week the epidemic was still on the increase in these regiments, and the incidence in the Engineer Officers' Training School was relatively high. However, there was a decline during the following week and the epidemic practically disappeared in a few days after October 18. The largest number of cases in any day during the epidemic was 771 on October 3. Of these, 579 were reported

from the 7th Regiment. This organization had next to the highest incidence of any in the camp. It was natural to expect this as the men were not as well housed as were other organizations, and in addition they were all men who had been inducted into the service during September, among them being about 2,000 limited service men who did not possess the best stamina. The suddenness of the epidemic in the 7th Regiment is shown on Chart 1, the scale in that case being exactly the same as for the 3rd Regiment.

RELATION OF DUST AND WEATHER TO SPREAD OF INFECTION

During the epidemic there were many dusty days. This caused some comment among the officers and enlisted men of the camp and the inspector from Washington called attention to it, with a recommendation that some dust-laying preparation be sprinkled on the roads. The geographical distribution of the cases does not seem to indicate that dust was an active factor in the production of the disease. The service battalions, which are the closest to the 3rd Regiment and directly in line to receive their dust, did not suffer as greatly as did the 7th Regiment which is to the windward of the 3rd Regiment and at a considerable distance. (See map of camp.)

A number of persons have advanced the theory that the epidemic was due to weather conditions, laying emphasis on the mean temperature. Chart 3 shows the number of new cases each day, in solid lines, and in broken lines is shown the maximum and minimum temperatures as reported by the Weather Bureau in Washington. This is the Weather Bureau situated nearest Camp Humphreys. It will be seen from this chart that there is apparently no connection between the incidence of new cases and the weather conditions. The days on which there was the lowest temperature and the greatest range of temperature there were only a small number of new cases, nor was there an increase on the following days. The weather as a cause of disease has been overworked.

DISTRIBUTION OF CASES

The epidemic may be regarded as having started in the 3rd Regiment. The Engineer Officers' Training School and the 6th Regiment, which are directly across the parade ground from the 3rd Regiment, suffered very lightly from the epidemic. There is apparently very little intercourse between the members of these organizations and the 3rd Regiment. However, they would have been affected by the same atmospheric conditions as the 3rd Regiment, the prevailing winds being southerly. The location of these organizations is shown on the map of the camp.

Development Battalion No. 1, located at Belvoir, about one mile from the 3rd Regiment, shows a rate of 28.9 per thousand, which is one of the lowest in the camp. The low rate in this organization is without doubt directly due to the fact that the men there are practically quarantined, and there is very little mingling between them and the rest of the camp. An analysis of the 13 cases occurring in this battalion shows that 4 of them were men who had been in the Development Battalion less than 5 days. Three of these came originally from the 7th Regiment, and 1 from the 3rd Regiment. They were transferred into

TABLE IV

WEEKLY "INFLUENZA" INCIDENCE RATE PER 1000 IN MAIN WHITE ORGANIZATIONS

ORGANIZATIONS	WEEK OF SEPT. 13-20	WEEK OF SEPT. 21-27	WEEK OF SEPT. 28-OCT. 4	WEEK OF OCT. 5-11	WEEK OF OCT. 12-18	TOTAL PERIOD OF EPIDEMIC
2nd E. T. R.	5.4	25.9	44.6	12.9	0.0	90.5
3rd E. T. R.	30.0	167.7	49.3	16.9	4.4	286.
4th E. T. R.	0.0	17.6	34.2	29.7	0.8	74.
5th E. T. R.	4.0	76.5	49.7	21.5	5.1	160.
6th E. T. R.	3.3	4.2	0.0	5.2	27.4	25.4
7th E. T. R.	0.2	2.4	240.3*	47.4	4.5	267.
E. O. T. S.	1.5	0.7	11.6	41.0	26.2	87.7
All whites in Camp	5.8	41.9	94.9	28.1	6.8	177.0

*Over 30 per cent of this organization were limited service men who arrived at the camp about the 1st of September.

TABLE V

STRENGTH OF COMMAND OF SAPPER REGIMENTS AND WHITE DEVELOPMENT BATTALION. NUMBER OF CASES OF "INFLUENZA," AND CASE RATE PER 1000. OCTOBER 1 TO 18, 1918

ORGANIZATION	STRENGTH	NUMBER OF CASES OF INFLUENZA			TOTAL	RATE PER 1000
		Sept. 28-Oct. 4	Oct. 5-Oct. 11	Oct. 12-Oct. 18		
215th	582	19	34	1	54	93.
216th	216	10	3	4	17	78.7
217th	600	113	30	4	147	244.6
218th	642	95	35	4	134	208.2
219th	583	60	48	4	112	192.5
220th	549	45	28	2	75	136.3
Development Battalion No. 1	450	5	6	2	13	28.9

TABLE VI

AVERAGE WEEKLY STRENGTH OF COMMAND FOR MAIN WHITE ORGANIZATIONS FOR PERIOD OF EPIDEMIC

ORGANIZATION	WEEK OF SEPT. 13-20	WEEK OF SEPT. 21-27	WEEK OF SEPT. 28-OCT. 4	WEEK OF OCT. 5-11	WEEK OF OCT. 12-18	AVERAGE FOR PERIOD OF ENTIRE EPIDEMIC
2nd E. T. R.	3158	3085	2718	2791	2348	2820
3rd E. T. R.	2992	2690	3504	2840	1376	2680
4th E. T. R.	2395	1814	1113	1091	1031	1489
5th E. T. R.	4236	3817	3198	3115	2767	3425
6th E. T. R.	985	896	627	388	255	630
7th E. T. R.	6276	6116	4518	3569	3766	4849
E. O. T. S.	1339	1469	1639	1732	1754	1587
All Whites in Camp	22393	21400	20848	22196	19597	21287

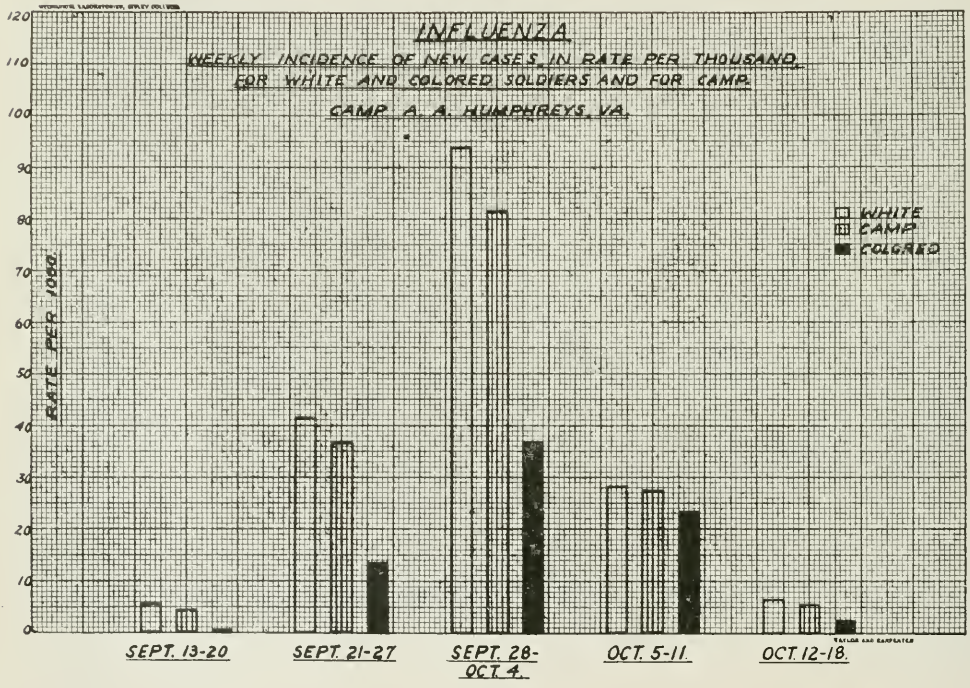
the battalion on the 27th and 28th of September, at a time when there was considerable "influenza" in both of these regiments and incidence was rising. That these cases brought the "influenza" with them can not be questioned. The first cases appeared in this organization on October 2 and 3, on which days there

were 6 cases. All of the 4 cases recently transferred appear on the infirmary record of this date. The 3 from the 7th Regiment developed exactly 4 days from the time they joined the organization. The other man from the 3rd Regiment was taken sick within 5 days after his transfer. All other men who were taken with "influenza" had been in the battalion at least 10 days.

Table IV shows the incidence rate per thousand in the principal white organizations of the camp for the five-week period of the epidemic. This also shows the incidence of new cases by weeks.

Six sapper regiments were organized during the epidemic and were made up from men from various organizations about the camp. They are considered

CHART 4.



by themselves, and the incidence of the disease in these organizations is given in Table V. It is difficult to classify the data from these organizations as they undoubtedly brought the infection with them and they vary greatly in strength. The 216th Sapper Regiment, for instance, had 216 men, while some of the other organizations were much larger.

Table VI shows the average weekly strength of the command for the principal organizations of the camp, and the average strength for each organization in the camp. This is the data from which the rate tables have been constructed. In some of the regiments, for instance the 3rd and 5th, the infirmaries served other smaller organizations. In such cases the strength of those additional organizations and the number of sick are included in the regimental strength and their morbidity tables. In determining the rates and the

floor space in the barracks, these facts are kept in mind and are considered with the organization.

Table VII deals with the actual number of cases each week in the white organizations and accounts for 3,771 of the cases in the camp. This table shows that the maximum for the 3rd and 5th Regiments occurred in the 2nd week, and for the 2nd, 4th and 7th Regiments in the 3rd week, the maximum for the Engineer Officers' Training School occurring in the 4th week, and the 6th Regiment in the 5th week of the epidemic.

INCIDENCE OF "INFLUENZA" IN COLORED ORGANIZATIONS

Chart 4 shows the weekly incidence of new cases in rate per thousand, for the white and colored troops. The data for this chart appear in Table IX. This chart is extremely interesting in view of the fact that it is generally considered that the colored race is far more susceptible to diseases of the respiratory tract than is the white race. The results of this epidemic show the exact reverse. The colored troops show a decidedly lower rate than the white troops all during the epidemic. The total rate is much lower and the weekly totals are also lower.

TABLE VII

WEEKLY NUMBER OF NEW CASES OF "INFLUENZA" IN MAIN WHITE ORGANIZATIONS FOR PERIOD OF EPIDEMIC

ORGANIZATION	WEEK OF SEPT. 13-20	WEEK OF SEPT. 21-27	WEEK OF SEPT. 28-OCT. 4	WEEK OF OCT. 5-11	WEEK OF OCT.12-18	TOTAL PERIOD OF EPIDEMIC
2nd E. T. R.	17	80	122	36	0	255
3rd E. T. R.	90	451	173	46	6	766
4th E. T. R.	0	32	38	31	9	110
5th E. T. R.	17	293	159	67	14	550
6th E. T. R.	3	4	0	2	7	16
7th E. T. R.	1	15	1089	169	17	1291
E. O. T. S.	2	1	19	71	46	139
Development Battalion			5	6	2	13
All Whites* in Camp	130	893	1978	632	133	3771

*Includes other small organizations not mentioned in Table.

Table VIII gives rates for the colored organizations.

TABLE VIII

INCIDENCE OF "INFLUENZA" IN COLORED ORGANIZATIONS FOR PERIOD OF EPIDEMIC. SEPTEMBER 13 TO OCTOBER 18, 1918

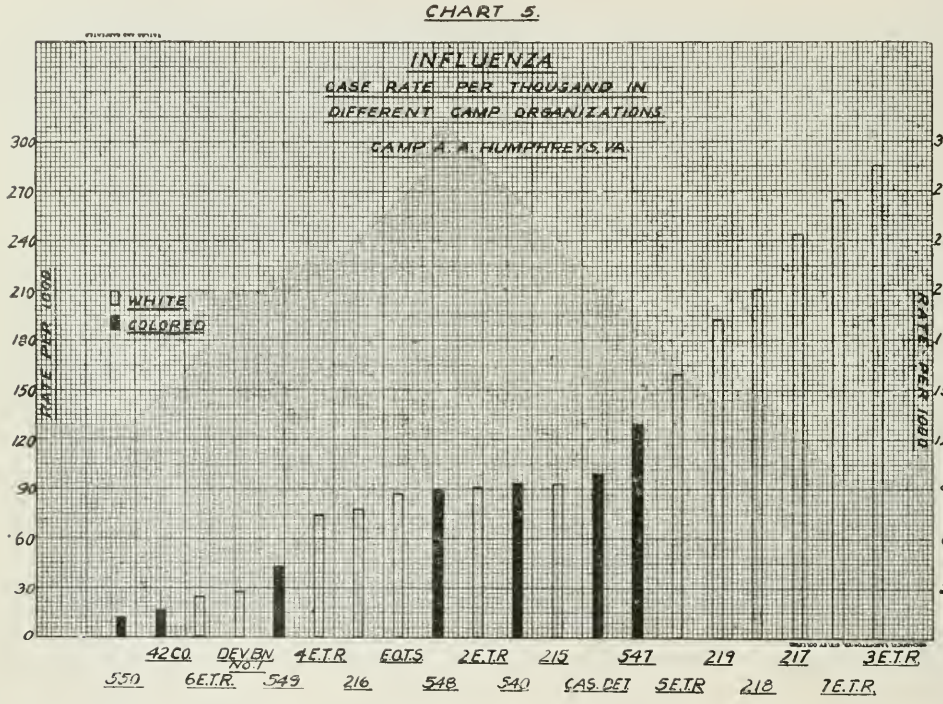
ORGANIZATION	AVERAGE STRENGTH OF COMMAND	TOTAL CASES	CASE RATE PER 1000
Casual Detachment	1487	147	99.
540th Service Bn.	916	85	92.8
547th Service Bn.	1002	129	129.
548th Service Bn.	894	80	89.6
549th Service Bn.	301	13	43.2
550th Service Bn.	628	8	12.7
42nd Separate Co.	250	4	16.0

Table IX

Weekly Incidence of New Cases of "Influenza" in White and Colored Troops. Rate per 1000

RACE	ENTIRE PERIOD	WEEK OF SEPT. 13-20	WEEK OF SEPT. 21-27	WEEK OF SEPT. 28-OCT. 4	WEEK OF OCT. 4-11	WEEK OF OCT. 12-18
White	177.0	5.8	41.9	94.9	28.1	6.8
Colored	76.0	0.6	13.7	36.8	23.4	2.8
Entire Camp	154 1	4.6	36.7	81.4	27.4	5.8

Chart 5 shows the rate per thousand for the different organizations in the camp. It varies a little from the data shown in Chart 4, in that certain of the



colored organizations are higher than some of the white organizations. However, the chart coincides with the data shown on Chart 4. The highest rate in the colored organizations, the 547th Service Battalion, is far less than the rate in the 5th, 7th or 3rd Regiments, and only slightly in excess of the incidence in the Engineer Officers' Training School and the 4th Regiment. A very interesting comparison in this chart is between the 42nd Company, which is colored, and the Engineer Officers' Training School and the 6th Regiment. These organizations are all quartered in the same area. They are under practically the same discipline and the same medical treatment. There can be, therefore, very little error regarding the diagnosis and difference in methods of living and diet received by these men. The 42nd Company shows the lowest rate in the entire camp, excepting the 550th Service Battalion. The comparison between the 550th Bat-

talion and the 42nd Company is not exactly just, because the 550th Battalion was just organized and did not exist in the early days of the epidemic.

Table IX shows in tabulated form the same data as appeared on Chart 4. Here we see that the rate among the colored troops is much lower than the rate among the white troops until next to the last week when they approached the white organizations closely. The entire period shows a difference in rate of something over 101 per thousand. This means that the incidence among colored troops was only 43 per cent of that among whites. These considerations call for a revision of our opinions as to the susceptibility of the colored race to diseases of the respiratory tract. There were 7 colored organizations in the camp during a considerable part of the epidemic; the rate varies considerably in these. We have already discussed the low rate in the 42nd Company which apparently is due to careful prophylaxis, including larger floor space and the use of cubicles. The 547th Service Battalion shows the highest rate among colored troops. This Battalion was divided into two parts, one part living about seven miles from the camp on the Telegraph Road doing road work. Through an oversight this organization was for a considerable time without medical attention. It had become thoroughly infected before any systematic measures of prevention were instituted and I believe this fact has to do with the large rate in that organization. Three of the Battalions have almost identical rates and the 549th and 550th Battalions with their low rates are probably due to the fact that these organizations were not organized at the beginning of the epidemic and the large number of men who developed the disease in the beginning were credited to the organization to which they were attached.

HOUSING

The general difference between the white and colored troops in this camp is in their housing. All the white troops are now housed and have been for some time in cantonment buildings which allow on the average 50 square feet of floor space per man. The colored troops, on the other hand, with the exception of the 42nd Company, are housed in tents. At the beginning of the epidemic there were six men in a tent, but later the number was reduced to five. It would seem but natural that life in a tent in the summer months, with better ventilation and more time in the open air, would cause a lower rate than where men are housed in barracks that are not as well ventilated. The experience of living in tents, however, does not make one believe that the ventilation is particularly good in tents. The 42nd Company was housed under exactly the same conditions as are the white troops of the Engineer Officers' Training School and the 6th Regiment. It would therefore seem to indicate that the colored race when living under good hygienic conditions is not as susceptible to "influenza" as the white race under the same conditions.

Chart 6 shows in black the "influenza" rate in the principal white organizations in the camp. This chart is based on the data in Table X. In white is shown the floor space allowed each man in each organization. It is not proper or just to attribute the differences shown here alone to the amount of floor

CHART 6.

INFLUENZA

RELATION BETWEEN FLOOR SPACE PER PERSON AND INCIDENCE RATE PER THOUSAND IN DIFFERENT CAMP ORGANIZATIONS.

CAMP A. A HUMPHREYS, VA
1918

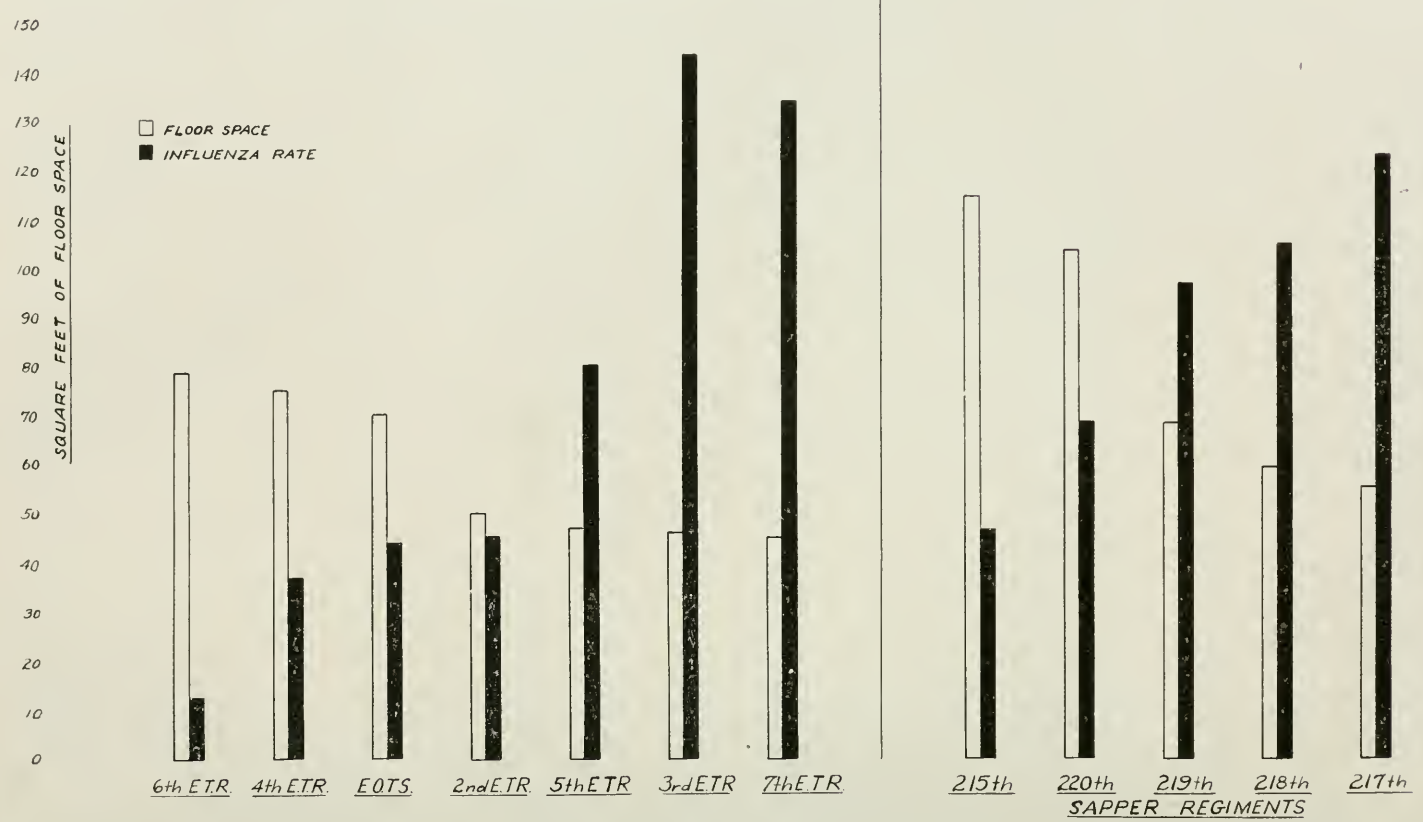


TABLE X

NUMBER OF PERSONS PER BARRACKS BY DIFFERENT ORGANIZATIONS. SQUARE FEET OF FLOOR SPACE PER PERSON, AND "INFLUENZA" RATE PER 1000

ORGANIZATION	NUMBER OF BARRACKS	NUMBER OF MEN PER BARRACKS	NUMBER OF SQUARE FEET OF FLOOR SPACE	INFLUENZA RATE PER 1000
6th Regiment	15	42	78.5	25.4
4th Regiment	34	44	75.	74.
E. O. T. S.	34	47	70.	87.7
2nd Regiment	43	66	50.	90.5
5th Regiment	49	70	47.	160.
3rd Regiment	42	72	46.	286.
7th Regiment	52	73	45.	267.
		"SAPPER REGIMENTS" (NEWLY FORMED)		
215th	17	29	114.	93.
220th	17	32	103.	136.3
219th	12	49	68.	192.5
218th	12	56	59.	208.2
217th	10	60	55.	244.6

space allowed each organization, but it certainly points very strongly to the fact that the incidence of the disease varied with the density of the population, although not with mathematical regularity. These figures are not mathematically accurate, as it was impossible at the time the table was constructed to get the exact figures as to the number of men that occupied each barracks during the epidemic. It was therefore necessary to average the conditions found in each organization. The least incidence appeared in the 6th and 4th Regiments and the Engineer Officers' Training School. In addition to the increased floor space, these regiments had for a long time been provided with curtains hanging between the individual beds in the barracks, thus making a cubicle for each man. Without doubt this largely reduced the incidence of infection in these regiments. However, the floor space does have a very important bearing on the case, because during the day these curtains are quite frequently rolled up and where large numbers of men are crowded in a barracks they naturally come into very close contact with each other during the hours they are not on the drill field. It might be said that during the epidemic every endeavor was made to keep the men in the open air as much as possible.

Considering the cases further, we find there is very little difference between the floor space in the 2nd and 5th Regiments, and yet there is a large difference between the rates for these regiments. This same apparently disproportionate difference in rates may be said to exist for the 5th, 3rd and 7th Regiments. As mentioned before, other factors help to account for these differences. However, in considering the 7th Regiment and the 5th Regiment it is to be remembered that these regiments contain many men who have been in the service but a short time and the 7th Regiment contains about 2,000 men physically more or less unfit for the service. The 3rd Regiment was early infected and many of the men came down before our plan of combat was fully developed, which no doubt accounts for the great number of cases in that Regiment. It may also be

said that during a considerable part of the epidemic there was not the same amount of activity among the medical officers of the 3rd Regiment as in some of the other regiments.

DISH WASHING AND "INFLUENZA"

It has been suggested that the disease is spread through the mess pans and other dishes. That there is some ground for this belief is not denied. The washing of dishes in the company mess halls has never been satisfactory and early in the epidemic efforts were made to improve conditions, resulting in an attempt to sterilize being made by most of the organizations. However, a study of the disease in the 2nd and 3rd Regiments with the question in mind, does not convince one that the dishes were responsible for the spread of the disease in this camp.

COMPLICATIONS OF "INFLUENZA" WITH PNEUMONIA

"Influenza," uncomplicated, is not a cause of death. The records here show four deaths from "influenza." I am of the opinion that the causes were really bronchopneumonia that could not be recognized by our methods of diagnosis.

Of the 4,237 cases of "influenza" considered in this report, 1171 developed pneumonia of one form or another, a percentage of 27.6. Of the pneumonia cases, 94 were lobar with 23 deaths, a percentage of 24.5; 1077 were broncho with 390 deaths, a percentage of 36.2. The mortality from all cases was 35.2 per cent.

Table XI shows the number of cases of pneumonia and the deaths by weeks.

TABLE XI

NUMBER OF CASES OF PNEUMONIA AND DEATHS FROM PNEUMONIA

WEEK OF	LOBAR PNEUMONIA		BRONCHO PNEUMONIA		TOTAL	
	Cases	Deaths	Cases	Deaths	Cases	Deaths
September 13-20	13	3	14	0	27	3
September 21-27	11	3	75	6	86	9
September 28-Oct. 4	40	6	423	81	463	87
October 5-11	24	6	470	207	494	213
October 12-18	4	5	73	79	77	84
October 19-25	2	0	22	17	24	17
Total Period of Epidemic	94	23	1077	390	1171	413

TABLE XII

WEEKLY DEATH RATE PER 1000 FOR PNEUMONIA FOR PERIOD OF "INFLUENZA" EPIDEMIC

WEEK OF	STRENGTH OF CAMP COMMAND	NUMBER OF CASES OF PNEUMONIA	NUMBER OF DEATHS FROM PNEUMONIA	DEATH RATE PER 1000 FROM PNEUMONIA
September 13-20	29210	27	3	0.13
September 21-27	26230	86	9	0.34
September 28-Oct. 4	27136	463	87	3.21
October 5-11	28518	494	213	7.48
October 12-18	26053	77	84	3.22
October 19-25	22688	24	17	0.75
Total Period	26637	1171	413	15.5

TABLE XIII

PNEUMONIA CASES AND INCIDENCE PER 1000, BY CAMP ORGANIZATIONS

SEPT. 13 TO OCT. 25, 1918

(WHITE)

ORGANIZATION	STRENGTH OF COMMAND SEPT. 13 TO OCT. 18	NUMBER OF CASES OF PNEUMONIA		TOTAL	INCIDENCE RATE PER 1000	TOTAL "INFLUENZA" CASES	PER CENT OF "INFLUENZA" CASES TREATED IN HOSPITAL	RATIO BETWEEN PNEUMONIA AND "INFLUENZA" CASES
		LOBAR	BRONCHO					
2nd E. T. R.	2820	8	50	58	20.6	255	39.3%	1:4.4
3rd E. T. R.	2680	17	112	129	48.2	766	39.1	1:5.9
4th E. T. R.	1489	2	28	30	20.2	110	45.5	1:3.7
5th E. T. R.	3425	13	132	145	42.4	550	34.4	1:4.2
6th E. T. R.	630	0	9	9	14.3	16	94.0	1:1.6
7th E. T. R.	4849	20	314	334	69.0	1291	24.8	1:3.9
E. O. T. S.	1587	3	53	56	35.2	139	68.0	1:2.5
215th Sapper Regt.	582	0	15	15	25.8	54	31.5	1:3.6
216th Sapper Regt.	216	0	9	9	41.6	17	17.6	1:1.8
217th Sapper Regt.	600	0	23	23	38.3	147	16.3	1:6.4
218th Sapper Regt.	642	1	14	15	23.4	134	24.6	1:8.5
219th Sapper Regt.	583	0	24	24	41.2	112	21.6	1:4.7
220th Sapper Regt.	549	1	11	12	21.8	75	30.7	1:6.2
1st Development Bn.	450	1	11	12	26.7	13	100.0	1:1.8
Miscellaneous White Organizations		4	32	36				
TOTAL WHITE	21287	70	837	907	42.6	3771	34.9	1:4.2

(COLORED)

Casual Detachment	1487	7	55	62	41.7	147	71.5	1:2.4
540th Service Battalion	916	3	41	44	48.1	85	53.0	1:1.9
547th Service Battalion	1002	5	73	78	78.	129	62.8	1:1.7
548th Service Battalion	894	4	28	32	35.8	80	42.6	1:2.5
549th Service Battalion	301	0	7	7	23.3	13	69.2	1:1.9
550th Service Battalion	628	0	8	8	12.7	8	100.0	1:1.0
Miscellaneous Colored Organizations		3	30	33		4		
TOTAL COLORED	6143	22	242	264	43.0	466	62.	1:1.8
TOTAL CAMP	27430	92	1079	1171	42.7	4237	38.%	1:3.6

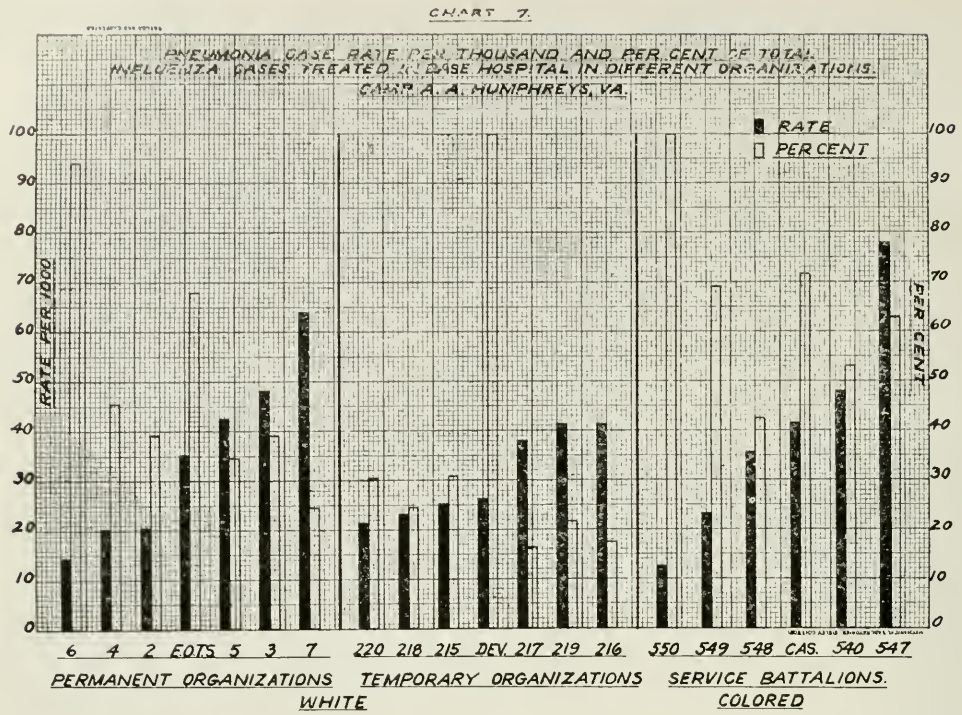


Table XII shows the deaths from pneumonia by weeks, and the total death rate from the complication.

Pneumonia is always more fatal among the colored race, but in view of the low incidence of "influenza" among the colored troops it was expected that pneumonia would show a correspondingly low rate. A study of the incidence of pneumonia in all the organizations of the camp was made and is shown in Table XIII. In it are columns showing the percentage of cases of "influenza" treated in the hospital, and the ratio between pneumonia and "influenza."

Among the white troops the incidence of pneumonia appears to vary with the density of population. This table shows also that the incidence of pneumonia is much higher among the colored troops although the percentage of cases of influenza in the hospital was much greater.

The relation between hospitalization and incidence of pneumonia brought out in a recent paper, is not apparent here. The 6th Regiment, with a low incidence of "influenza" and with 94 per cent of the cases treated in the hospital, shows a ratio between pneumonia and "influenza" of 1 to 1.6. The same is shown in the colored organizations.

I, however, do not take issue on the question, because it is difficult to disentangle the various factors which produce the conditions observed in this epidemic. A factor that played a big part in this camp was the high morale of the men, which made them attempt to fight the disease. Many such cases developed pneumonia, especially in the Engineer Officers' Training Camp and the 6th Regiment.

The relation between pneumonia and hospitalization is shown on Chart 7.

CONCLUSIONS

The result of this study seems to indicate:

1. That the incidence of the disease increases with the density of population in barracks.

2. That the hanging of a sheet between the individual beds in the barracks was of value in preventing infection.

3. That the negro race suffered much less from the disease than did the white.

4. That there were more cases complicated with pneumonia among the colored troops and that the disease was more fatal among them.

The charts and statistical data were compiled under my direction by Sergeant Joseph Herzstein, Medical Department.

APPENDIX

A

ARTICLE IN CAMP NEWSPAPER "THE CASTLE," SEPT. 8, 1918

We have heard a great deal recently regarding the so-called "Spanish Influenza.' Influenza is a disease that has been known in this country for about 100 years. Every once in a while it becomes epidemic and spreads all over the country. One of the most noted epidemics this country has ever had was in 1889 and 1890. It is more prevalent in the winter months, although not unknown in the fall and spring months. In itself influenza is not particularly serious. It, however, so reduces the resistance of the person that not infrequently he becomes the victim of other diseases such as pneumonia and tuberculosis. The mortality from influenza is usually due to one of those diseases, or to diseases of the heart which may accidentally be associated with influenza. At the present time influenza is becoming very prevalent in the United States. Recent reports from some of the camps show that several thousand cases of this disease developed within one or two weeks.

Influenza is a communicable disease and is transmitted from one person to another through the medium of the fine spray thrown out from the nose or throat during coughing or spitting. It can easily be controlled. It does not depend upon the weather nor upon dampness. It is more common in the winter time because at that season persons are more likely to congregate in badly ventilated rooms and come in closer contact with their fellows.

The prevention of the disease is simple and consists of avoiding the disgusting habit of coughing into another's face. It is very probable that this camp may during the coming fall or winter be visited by an epidemic of this disease. We will be able to control it if every man in the camp will do his part. His part will not require any work or hardship. It simply means that the individual must hold before his mouth and nose each time he coughs, a handkerchief or a piece of newspaper. In case paper is used it should always be burnt as soon as possible. Men should also avoid spitting on the floor or coughing in the air.

Do your part to prevent this disease and by so doing help keep Camp Humphreys "First in Health!"

B

War Department
Headquarters, Camp A. A. Humphreys,
Virginia.

September 18, 1918.

Memorandum No. 399.

1. During the past winter the principal diseases encountered by the American troops in camps in the United States, were diseases spread through the excretions of the respiratory tract, including the mouth. These diseases include: Pneumonia, Influenza, Bronchitis, Cerebrospinal Meningitis, Measles, and Scarlet Fever. Without doubt there are carriers of all these diseases in the different organizations of this camp. At the present

time we are unable to discover these men. It is therefore necessary to take precautions as far as possible to limit the spread of these diseases, and the following instructions will be complied with:

2. On the left side of each bed in the barracks a shelter half will be hung. This can be readily accomplished by placing a long stick at the head, and a short stick at the foot of the bed. This arrangement of the beds will greatly diminish the chances of infection.

3. All the enlisted men of the camp will attend a lecture on the spread of these diseases, on the following schedule:

Wednesday at	5 P.M.	The entire 7th Regiment.
"	" 7 P.M.	The entire 5th Regiment.
Thursday	" 5 P.M.	The entire 4th Regiment.
"	" 7 P.M.	The entire 2nd Regiment.
Friday	" 5 P.M.	The Officers' Training Class.
"	" 7 P.M.	The entire 3rd Regiment.
"	" 8 P.M.	The entire Service Battalions, including Casual Camp and Sanitary Bns.

4. One officer must accompany each organization.

By command of Brigadier General Kutz:

John E. Harris,
Major, C. E.
Adjutant

C

War Department
Headquarters, Camp A. A. Humphreys,
Virginia.

September 27, 1918.

Memorandum No. 436.

Regimental Commanders, Battalion Commanders, and Commanding Officers of Detachments will see to it that Company Commanders personally supervise the falling out of all men at Reveille and Retreat formations who appear to have colds. These possible cases will be specifically called for and sent to Regimental Surgeon to determine whether or not they have Spanish influenza.

By command of Brigadier General Kutz:

George Mayo,
Major, C.E.
Actg. Adjutant.

D

Office of Camp Surgeon
Camp A. A. Humphreys, Va.

September 30, 1918.

Memorandum to All Regimental and Battalion Surgeons and Surgeons of the Base Hospital:

1. The Surgeon General directs that during the present emergency all cases of infectious diseases, including influenza and colds, be so arranged in wards that each man shall have 100 square feet of floor space. If the wards now assigned to you are not sufficient for this purpose, make requisition on the Commanding Officer of your unit for additional space.

2. As it is difficult to determine whether men with coryza are coming down with influenza or not, you are directed to, as far as possible, have all men with colds report to the Infirmary twice a day, and instill into the nostrils of each man two drops of a 10 per cent solution of Argyrol or similar silver salt.

E

War Department
Headquarters, Camp A. A. Humphreys,
Virginia.

Sept. 30, 1918.

Memorandum No. 449.

Organizations will draw six (6) feet of sheeting from the Quartermaster for each member of organization. This is for the purpose of constructing screens to be placed between cots as directed by the Surgeon. Organizations will supply all other material themselves. Installation will be completed as soon as possible.

By command of Brigadier General Kutz:

George Mayo,
Major, C.E.
Actg. Adjutant.

F

War Department
Headquarters Camp A. A. Humphreys,
Virginia.

October 3rd, 1918.

General Order No. 15

1. In view of the serious epidemic of Spanish influenza at this camp and upon the recommendation of a special investigating officer from the office of the Surgeon General, the following precautions will be strictly observed in all organizations.

No more than five occupants to a pyramidal tent will be permitted. All windows in barracks will be kept open full width from Reveille to Retreat. All except those on the windward side will be kept open from Retreat to Taps, and from Taps to Reveille all windows will be kept at least one-half way open. Compliance is again directed to Memorandum No. 399, which states that shelter halves will be stretched on one side of each cot for its full length. This practice has not been fully carried out in some of the regiments. Company commanders will be responsible for the inspection of barracks by an officer between Taps and Midnight, and will submit with their morning report a written statement of conditions found in each building at time of inspection. Further, the Officer of the Day or the Officer of the Guard will make an inspection of barracks between Midnight and Reveille, and submit a written report, with the guard book, of conditions found in each building at time of inspection. Regimental commanders will require reports each day regarding the enforcement of these regulations by the officers responsible for the inspections.

2. It has been noticed, lately, that fly-paper is not used in some of the Messes in this camp, and as a consequence, there are a large number of flies in their messes. Strenuous efforts will be made to reduce the number of flies.

3. Methods of washing dishes in most Messes are not such as to insure adequate cleanliness and sterilization. Steps will be taken after each meal so that all dishes will pass through boiling water.

4. Where barracks are used exclusively for the care of the sick, means will be taken of providing these Messes with a suitable light diet.

5. Every effort will be made to reduce the use of common drinking cups.

6. Efforts will be made to prevent the men from congregating in crowds, particularly indoors. In all exchanges of this camp steps will be taken to post men at the entrance so as to prevent crowding and in the general assembly halls only enough men will be admitted so that not more than every other seat will be occupied.

By command of Brigadier General Kutz:

George Mayo,
Major, Engineers.
Acting Adjutant.

G

Office of Camp Surgeon,
Camp A. A. Humphreys, Va.,

October 4, 1918.

Memorandum to All Medical Officers:

1. The Surgeon General directs that all the men who have suffered from influenza be kept off duty for at least ten days after their temperature has reached normal. This, however, does not mean that the men need remain in the Base Hospital. They may be carried in quarters, but kept at rest and under good care during these ten days. The object of this is to cut down instances of pneumonia following influenza.

2. The inspection made on October 3rd by Colonel Chamberlain, M.C., showed the following defects, which should be remedied immediately:

(a) Not all the patients were in cubicles.

(b) There were a great many flies in kitchens and in buildings where patients with influenza were being treated.

(c) In not a few instances men had expectorated on the floor. Colonel Chamberlain suggested that a newspaper be placed on the floor near the bed, and spit cup placed on it. The whole should be burned at frequent intervals during the day. Newspapers are plentiful in the camp and there should be no difficulty in getting them.

(d) The condition of the floors of some of the buildings was not satisfactory, being littered with dirt and in some cases unconsumed food. All floors should be swept several times a day with damp sawdust, which should be later burned. Special attention should be paid to keeping floors clean and to prevent remnants of food from being thrown about the buildings.

(e) In some cases it was found that men were receiving food which was not satisfactory. In most of the companies the mess fund is in excess of the amount allowed by camp orders, and therefore there should be no difficulty in making whatever extra purchases are necessary in order to properly subsist the sick in the camp. These surgeons should pay particular attention to this. Where the medical detachment is running a mess you can not call upon the company for additional subsistence under these circumstances.

3. If there are not sufficient line men detailed for duty in the wards, make requisition to the Regimental Commander for the number needed.

4. The Surgeon General has directed that all patients transferred to the Base Hospital by ambulance be masked. Until such time as we are able to obtain a sufficient supply of masks from the Red Cross, you are directed to make handkerchief masks from cheese cloth. These masks are not to be destroyed when once used, but are to be returned to the infirmary and washed with soap and water and sterilized.

I. W. Brewer,
Lt. Col. M.C.
Camp Surgeon.

H

War Department
Headquarters, Camp A. A. Humphreys,
Virginia.

October 8, 1918.

Memorandum No. 485.

1. No more than five men will be allowed to occupy a pyramidal tent. The number of men in Barracks will not exceed the authorized number for each building. Standard Barracks in this camp provide accommodations for 66 men, at the rate of 50 sq. ft. of floor space for each man. This number will not be exceeded. All barracks will be aired each day by opening all the windows. At night at least one-half of all the windows will be kept open. Tents will be furled on every sunny day. The ventilators at the top of tents will be kept open. Where tin hoods are provided for ventilation, they will be arranged so as to leave 2 inches between the bottom of the canvas and the tin hood. During the present epidemic all bedding will be aired and sunned daily. Cubicles in accordance with previous orders will be provided for every man, whether in tents or in barracks. Sheeting for this purpose can be procured from the Quartermaster.

2. In sweeping the Barracks every effort will be made to diminish the amount of dust. There is a large amount of clean sawdust in the camp. It should be procured and placed in a dry place and dampened and used for sweeping. This will practically eliminate all dust.

3. Special attention will be paid to flies. Fly paper, fly traps, and swatters will be used. If the Quartermaster has not a sufficient number of fly traps they can be easily improvised from plans which can be obtained from the secretary of the Schools. Swatters can be easily made from waste screening.

4. Commanding Officers of organizations will see that mess utensils are thoroughly sterilized after being used. Where enamelware is provided it should be collected in tubs and boiled. Where individual mess kits are used an abundance of very hot water should be provided. It has been noticed in a large number of cases that water for washing dishes has been practically stone cold and very dirty before the last men have washed their dishes.

5. The officer present at the mess will, before each meal, caution all men of the danger of coughing while at meals. Men who cough will be sent from the mess hall and required to eat their meals by themselves at a later time.

6. At least 4 noncommissioned officers will be detailed for duty at each Y. M. C. A. building each evening. They will report one-half hour before each entertainment and remain until the entertainment is over. Their duties will be to enforce the regulations regarding coughing and crowding. Men who cough will be excluded from buildings, unless they are using proper precautions. Not more than every other seat in the building will be occupied, in both directions. In other words, no man will sit in close proximity to another. Exchange officers will see that no more men are allowed to enter the exchange at one time than may stand at the various counters. Crowding of men around the counters will thus be prevented.

7. Every effort will be made to keep the men out of doors during the entire day. They will be given such drill and other instructions as may be necessary. Company Commanders will, however, avoid strenuous exercise, as at this time it is not wise to have the men become tired or overheated.

In the sections where hot water is not provided in the bath houses, arrangements will be made with the Commanding Officer in adjacent areas for use of the bathing facilities there at specified times. Every man should have a bath at least once a week, and twice a week if possible.

8. Company Commanders will report immediately to the surgeon any man who apparently is sick. Sick men will not be kept in the same quarters with the well, unless the surgeon certifies that illness is of a nature that will not be transmitted. All officers who are sick will immediately report to the surgeon for examination. Surgeons will send to the Base Hospital all officers suffering from symptoms of influenza. The noncommissioned officer in charge of Barracks will see that the regulations regarding spitting in and about the Barracks are carefully observed.

By command of Brigadier General Kutz:

George Mayo,
Major, C.E.
Acting Adjutant.

THE SALICYLATES. X. THE SPECIFICITY OF SALICYLATE IN RHEUMATIC FEVER*

By Paul J. Hanzlik, M.D.; R. W. Scott, M.D.; and P. C. Gauchat, M.D., Cleveland, Ohio

ASIDE from the striking symptomatic relief, the claim for the specificity of salicylates in rheumatic fever lacks scientific evidence. Some of the theories for the alleged specificity have been recently tested and found wanting.[1] The reported beneficial effects of other procedures, such as the foreign protein therapy of J. L. Miller,[2] rest, and others in the treatment of rheumatic fever tend to weaken rather than support the arguments for specificity both as to etiology and symptomatic relief. Owing to the uncertainty of the etiology of rheumatic fever it is manifestly impossible to investigate the specificity of salicylate with any satisfaction or convincing accuracy from this standpoint. This limits us practically to a study of the symptoms.

Essentially, the problem resolves itself into a comparison of the therapeutic effects of salicylate with other agents chemically different, but possessing similar pharmacologic actions. Two methods of approach may be utilized for this: 1. A statistical study of series of cases receiving the different forms of medication may be made. Such a study is very tedious and requires a large number of cases. It has the advantage that the elements of rest and natural recovery may be more satisfactorily controlled. 2. A careful study of the effects of both types, i. e., salicyl and nonsalicyl medication in the same individual should be able to yield equally important, interesting and conclusive results. This is not so time-consuming and requires a smaller number of individuals. However, the disadvantage of the elements of rest and natural recovery must be reckoned with in the terminal medication, and are not so easily eliminated. On the other hand, if recovery occurs without terminal medication, which in our series always consisted of salicylate, the argument against salicyl is conclusive. For the present, and because of convenience, we have used the individual experimental rather than the statistical method. All told, nine patients have been observed. Enough results have been obtained to justify a report of the progress of our work. Summarized protocols of all the patients are appended at the end of the paper.

METHOD

The patients were first treated with nonsalicyl medication, and if no relief was obtained within a reasonable period of time, as indicated by the progress of the condition, salicylate up to "toxicity" in the usual way was administered. That is, the antipyretic and analgesic properties of salicylate were imitated by combinations of other drugs such as morphine and quinine, which are chemically different from salicylate, but possess similar antipyretic and analgesic

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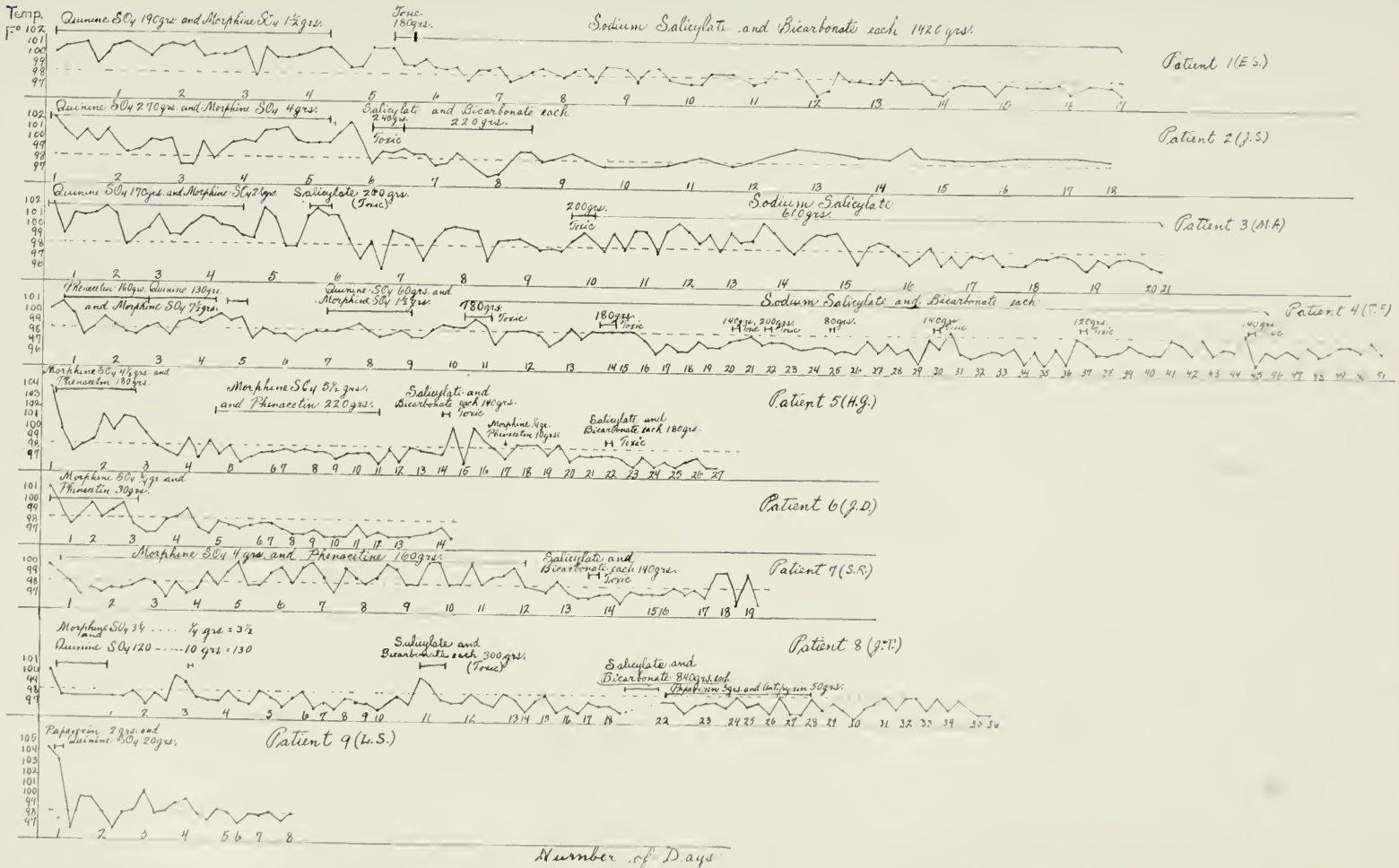

Fig. 1.—Effects of nonsalicyl and salicylate medication on the temperature in rheumatic individuals.

qualities. In this way, the symptoms could be readily combated, and if complete relief ensued without further medication, no specificity for salicylate, either etiologic or symptomatic, could be claimed. In addition, cathartic salts were frequently administered to avoid the constipating action of the opiates, for it was frequently observed that the maintenance of fever and constipation were associated, the patient otherwise being quite comfortable in many respects. "Complete relief" was judged by the prompt and permanent fall of body temperature

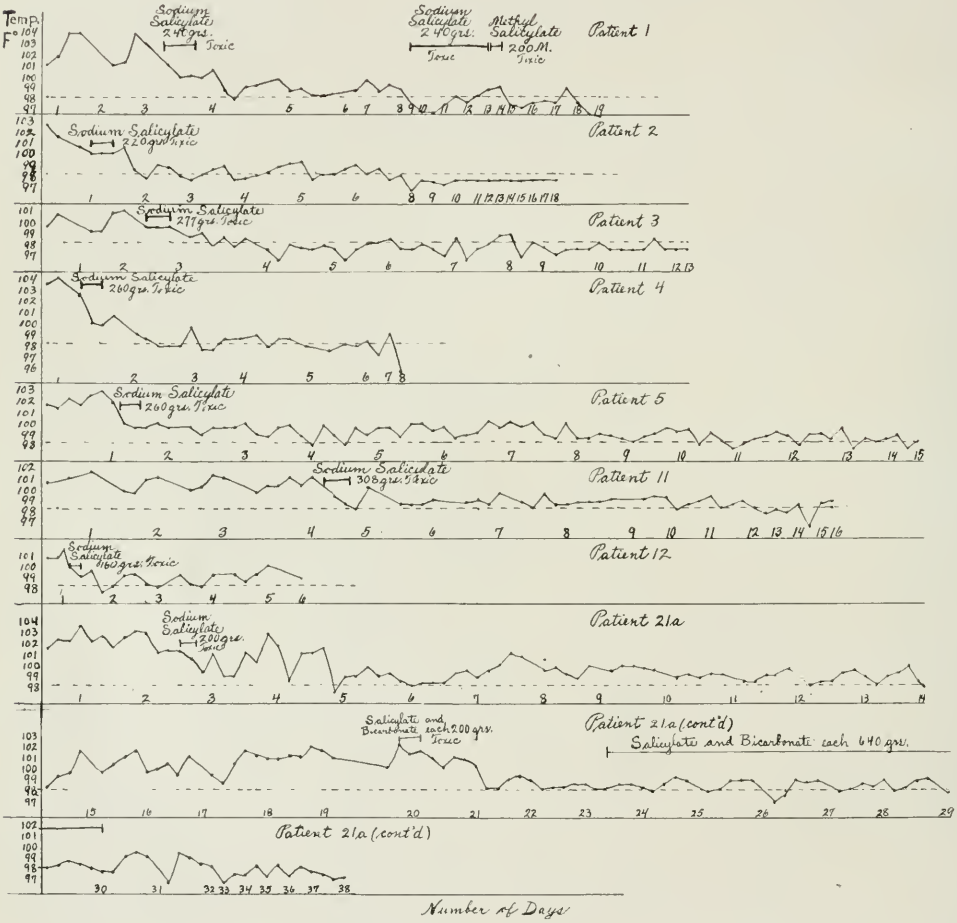

Fig. 2.—The effects of salicylate medication alone on the temperature in rheumatic individuals.

to normal, together with the disappearance of pain, redness, and swelling in the joints, and the restoration of general comfort. When only some of the symptoms were relieved, or all imperfectly, the relief was regarded as partial. When the symptoms persisted unabated, the result was called "no relief." On the whole, rather large doses, although variable, of opiates and the various antipyretics were used, and this is believed to be correct in principle, for it appears that the prompt relief generally obtained with salicylate is due to the marked effects of the very large doses used. Constriction of the pupil and slowing of the

respiration served as guides in the administration of the opiates, and changes in the pulse for the various antipyretics. Brief descriptions of the comparative effects of the two kinds of medication follow:

TEMPERATURE

This was promptly lowered in a majority [six, Patients 2 (J. S.), 4 (T. F.), 5 (H. G.), 6 (J. D.), 8 (J. T.), 9 (L. S.); Fig. 1] of all the patients by the nonsalicyl combinations, and also by salicylate (five patients, 1, 2, 3, 4, 5), although on the whole more effectively and permanently by salicylate. In four cases [patients, 6 (J. D.), 9 (L. S.), 8 (J. T.) and 5 (H. G.)] the temperature fell to normal and remained practically unchanged by the nonsalicyl medication. In four cases [3 (M. A.), 4 (T. F.), 5 (H. G.), 7 (S. R.)] the temperature had fallen to normal before the salicylate was administered, therefore the return of the temperature to normal can not be justly attributed as due to salicyl. In two cases [3 (M. A.) in part, and 8 (J. T.) entirely] the febrile temperatures persisted in spite of the administration of salicyl. It appears that once the fever has run its course it tends to abate in spite of the antipyretics used and seldom returns to the original level. Continuous though moderate medication with salicyl or other antipyretics during the period of convalescence, will, of course, tend to mitigate any tendency to a recurrence of the fever. This, as a matter of fact, is a common practice and undoubtedly contributes also to the general recovery of the individual.

Of the eight patients receiving salicylate alone (see Fig. 2), four (11, 12, 5, 21a) continued afebrile though variable temperature. In one (Patient 1) the temperature was reduced to normal and subnormal after repeated salicyl medication only. In the remaining three patients, single administrations of toxic doses of salicyl brought the temperature promptly and permanently within the normal range.

JOINT SYMPTOMS

Pain, tenderness, complaint of "soreness" when movements were attempted, and swelling were the most prominent and constant symptoms in our series before the administration of any medication whatsoever. These were completely relieved, though temporarily in some, in a majority [eight, Patients 1 (E. S.), 2 (J. S.), 3 (M. A.), 5 (H. G.), 6 (J. D.), 7 (S. R.), 8 (J. T.), 9 (L. S.)] of the patients while receiving nonsalicyl medication, and in two patients [6 (J. D.), 9 (L. S.)] no salicyl medication was necessary. The remaining patients [1 (E. S.), 2 (J. S.), 3 (M. A.), 4 (T. F.), 5 (H. G.), 7 (S. R.), 8 (J. T.)] received salicylate because some of the symptoms reappeared in more or less aggravated form after the nonsalicyl medication was stopped. Salicylate removed these symptoms completely in four patients [2 (J. S.), 1 (E. S.), 3 (M. A.), 7 (S. R.)], partially in two [4 (T. F.), 5 (H. G.)]. In two [5 (H. G.), 8 (J. T.)] cases salicyl was ineffective. To what extent the elements of rest and natural recovery contributed in finally obtaining relief during the salicyl régime can not be said, but certainly can not be disregarded. The salicyl periods are not strictly comparable with the nonsalicyl, for salicylate was admin-

istered continuously over a long period, while the nonsalicyl medication lasted only a comparatively short period. This could not be avoided for it was not certain in the beginning of the work if, when results were not satisfactory, during the nonsalicyl régime we were not really depriving the patients of benefits to be derived from salicylate. However, the satisfactory results in patients 6 (J. D.) and 9 (L. S.) obtained without any salicylate whatsoever entirely dissipated our fears, and conclusively demonstrated that complete therapeutic relief can be obtained on a régime of nonsalicyl medication. This completely discounts the claims of specificity of salicylate in rheumatic fever for the joint symptoms and fever at least.

Our records, when salicylate alone was used, are too incomplete to draw any definite conclusions. However, a study of the protocols indicates that salicylate promptly and effectively removed the joint symptoms in a majority of the patients, and this is in harmony with the usual experience. In two individuals (Patients 1 and 21a) it was necessary to repeat the administration of salicylate because the joint symptoms persisted.

GENERAL DISCOMFORT

Under this are included various complaints such as the subjective sensation of aching, weakness and stiffness in the limbs, restlessness, etc. All of the patients became more comfortable on the nonsalicyl combination, only one [4 (T. F.)] having complained of some discomfort. Two [6 (J. D.), 9 (L. S.)] became entirely comfortable without further (salicyl) medication.

With six of the patients receiving nonsalicyl medication discomfort returned and they became comfortable, though partially with one [2 (J. S.)], again on salicyl medication. Discomfort with one [8 (J. T.)] continued in spite of repeated administration of salicylate, general comfort being restored with nonsalicyl medication.

Our notes on the series in which salicyl alone was administered are incomplete.

CIRCULATION AND RESPIRATION

The tabulated results show that both the pulse and respiration were usually showed with the defervescence of the fever irrespective of the kind of medication, i. e., whether nonsalicyl combinations or salicylate, although there appeared to be a greater tendency to slowing of the respiration with the opiates. The differences were unimportant, and since these functions have no important bearing on the symptomatic relief in rheumatism, they need not be considered further.

It is well known that endocarditis, which is commonly associated with rheumatism, is not remedied by the administration of salicylate. This was true for our salicylate series, and the same also held for the nonsalicyl.

DURATION OF DISEASE

This will vary with the initial severity of the attack, multiple extension to joints, the individual, and other factors. Our series are too small to furnish

definite conclusions. However, a comparison of the nonsalicyl-salicyl with the salicyl alone series may be made. In the nonsalicyl-salicyl series seven patients [1 (E. E.), 2 (J. S.), 3 (M. A.), 4 (T. F.), 5 (H. G.), 7 (S. R.), 8 (J. T.)] the sojourn in the hospital ranged from 17 to 31 days, mean 24 days. Two patients [6 (J. D.), 9(L. S.)] receiving nonsalicyl medication alone sojourned only 8 and 19 days, respectively. With eight patients of the salicyl series the sojourn ranged from 6 to 38 days, mean 15 days. In general this would be favorable to salicylate. However, there were great variations, and a larger series would likely smooth out the differences. Assuming these results express the general tendency correctly it seems hardly possible that special claims to specificity of salicylate in rheumatism could safely rest on this criterion, for the sojourn is about as short on nonsalicyl medication alone as on salicylate alone, and the tendency to prolongation in the nonsalicyl-salicyl series, taking the cases individually is practically unimportant.

RECURRENCE OF SYMPTOMS

In 7 out of 9 patients whose initial medication consisted of various nonsalicyl combinations, symptoms of the disease recurred. Of these one [8 (J. T.)], however, was not benefited by salicyl treatment; and two patients had no recurrence after nonsalicyl medication. Of the salicyl series, consisting of 8 individuals, two required repeated salicyl treatment for a recurrence of the symptoms. It would seem, therefore, that treatment with salicylate alone from the beginning insures freedom from symptoms of the disease for a majority of patients, and this agrees with the usual experience; but it is also true that treatment with nonsalicyl combinations alone can render patients [see 6 (J. D.) and 9 (L. S.)] free of the symptoms. This does not point to any particular specificity of salicylate. The greater efficiency of the salicyl may be ascribed to the massive doses and prolonged treatment.

A summary of all the results as to dosage and therapeutic response in all the patients is presented in Table I.

DISCUSSION

From this study of the comparative effects of nonsalicyl and salicyl medication, it can not be concluded that salicylate possesses any unusual action or peculiar specificity in rheumatic fever. It is seen that prompt though partial relief was obtained in the majority of the patients receiving drugs other than salicyl. This is true for both early and late symptoms of the disease. In some of the patients the symptoms persisted despite salicyl medication, and in at least 4 cases (2 of nonsalicyl-salicyl series and 2 of salicyl) the condition recurred shortly after salicyl treatment. In those patients in whom the symptoms persisted, although considerably moderated, after treatment with nonsalicyl antipyretics and analgesics, salicyl appeared to give more permanent relief. On the other hand in two of the patients the fever persisted in spite of the salicyl medication. In some of the patients the persisting antipyretic effect during salicyl medication (although other symptoms of the disease were present) may be due to the retention or delayed action of the nonsalicyl antipyretic.

TABLE I

COMPARATIVE THERAPEUTIC RESPONSES OF RHEUMATIC INDIVIDUALS TO NONSALICYL AND SALICYLATE MEDICATIONS

PATIENT	NATURE OF THERAPY				
	NONSALICYL			SALICYLATE	
	DRUGS AND TOTAL DOSAGE		RELIEF	TOTAL DOSAGE	RELIEF
1 (E. S.)	Quinine 190 gr.	Morphine 1½ gr.	Partial	Sod. Salicylate 1600 gr.	Complete
2 (J. S.)	Quinine 270 gr.	Morphine 4 gr.	Partial	Sod. Salicylate 460 gr. $NaHCO_3$ 460 gr.	Partial
3 (M. A.)	Quinine 170 gr.	Morphine 2¼ gr.	Partial	Sod. Salicylate 1063 gr.	Partial
4 (J. F.)	Quinine 190 gr. Phenacetine 160 gr.	Morphine 9 gr.	Partial	Sod. Salicylate 1620 gr.	Partial
5 (H. G.)	Phenacetine 230 gr.	Morphine 5¾ gr.	Partial	Sod. Salicylate 220 gr.	Partial though more complete
6 (J. D.)	Phenacetine 30 gr.	Morphine ¾ gr.	Complete	None administered	
7 (S. R.)	Phenacetine 160 gr.	Morphine 4 gr.	Partial	Sod. Salicylate 140 gr.	More complete
8 (J. T.)	Phenacetine 130 gr. Antipyrin 50 gr.	Morphine 3½ gr. Papaverine 3 gr.	Temporarily complete Complete	Sod. Salicylate 840 gr.	None
9 (L. S.)	Quinine 20 gr.	Papaverine 2 gr.	Complete	None administered	

With four of the nine patients [1 (E. S.), 3 (M. A.), 4 (T. F.), 7 (S. R.)] unquestionably no effective and permanent relief from the symptoms of pain, fever, swelling of the joints, and general discomfort, was obtained until salicylate was administered. Eliminating the elements of time, rest, and natural recovery, it appears that the relief of later symptoms is brought about more effectively and permanently by salicyl than by combinations of drugs whose pharmacologic actions are similar, but different chemically.

The results of a previous statistical study[3] support the provisional conclusions drawn from the present work. It was found that about 18 per cent of the patients with rheumatic fever were incompletely or not at all relieved by the administration of salicylate in toxic doses. In the large majority that was relieved it is not known to what extent repeated salicyl medication was resorted to, but it is certain that salicyl was repeatedly administered to many patients. In addition, complete relief was obtained in a majority of individuals suffering with other diseased conditions, and whose etiology was either questionable or entirely different from rheumatic fever. That is, 53 per cent of cases of chronic rheumatism and 41.6 per cent of a miscellaneous variety of other conditions were completely relieved of their symptoms by the administration of salicylate in toxic doses. This favorable influence exerted by salicylate would

not, of course, deprive salicylate of its alleged specificity in rheumatic fever but the symptomatic relief (analgesia and antipyresis) produced by it is in line with that obtained in the treatment of rheumatic fever. It is conceivable at least that this is also the main contribution of salicylate in the generally practiced therapy of rheumatic fever.

CONCLUSIONS

The number of our cases is too small to draw definite conclusions. However, this much may be said, namely, that so far as the acute symptoms of rheumatic fever are concerned, these can be promptly and effectively relieved by combinations of antipyretics and analgesics chemically different from salicylate. It is also possible to obtain permanent relief with these. If to this are added the favorable reports of J. L. Miller with foreign protein and rest alone, and the numerous recurrences of the disease in patients repeatedly treated with salicylate in large doses, then it may be provisionally concluded that salicylate possesses no thoroughly demonstrated specific action in rheumatic fever. It is no more than a symptomatic remedy which can be safely administered in very large doses, and represents a fortunate combination of both antipyretic and analgesic qualities which makes it much more suitable, and, also desirable for the treatment of rheumatic fever than combinations of opiates and various antipyretics. The injurious effects of salicylate on renal function and the kidney[4] might be raised against the promiscuous and unwarranted use of the drug, but its efficiency and desirability as a symptomatic remedy in rheumatic fever may be regarded as outweighing the seriousness of these disturbances.

SUMMARIZED PROTOCOLS

Patient 1 (*E. S.*). *Female. Diagnosis*—rheumatic fever. Temperature on admission 100.4° F. Administered 180 grains of quinine together with 1½ grains of morphine during the first 5 days of illness. During this time the temperature was variable though generally slightly elevated with an improvement in general discomfort and freedom from pain and tenderness in the joints. On the sixth day there was general discomfort but no pain in the joints, the temperature remaining elevated. Salicylate to "toxicity" (180 grains) was administered, and was continued every four hours for the next 13 days, when the patient was discharged cured. During the salicyl period the patient was generally comfortable and free from joint pains and fever. The temperature gradually fell to the normal level and towards the end became subnormal. The total dosage of salicyl administered was 1600 grains.

It may be concluded that nonsalicyl medication, consisting of morphine and quinine, partially removed the symptoms of rheumatic fever the temperature remaining practically unchanged. This, together with the remaining symptoms were completely removed by prolonged treatment with salicyl.

Patient 2 (*J. S.*). *Diagnosis*—rheumatic fever. Temperature on admission 102.3° F. Administered 270 grains of quinine together with 4 grains of morphine during the first five days. The temperature gradually fell to 97.8° on the third day, and again gradually rose, reaching 102° at the end of the fifth day. During the time the temperature fell the patient was free from pains in the joints and was generally comfortable, but as the temperature rose symptoms of general discomfort together with marked pain in the joints originally affected returned. On the sixth day the patient was made toxic with 240 grains of salicylate, and the drug was continued every four hours for the next few days equivalent to about 220 grains, or a total of 460 grains of salicyl was administered. Pain in the joints and general discomfort promptly disappeared and the temperature fell to 97° F., and remained practically normal for the next four days, but on the twelfth day the temperature rose to 100°, and after that gradually fell to 99°, that is, the patient was

febrile to the end of the experiment. During this time there was general discomfort and the wrists and shoulders were painful until the 16th day. During the last two days the patient was comfortable without complaint of pain and was discharged on the 18th day.

Both the nonsalicyl and salicyl medications gave partial relief from symptoms of rheumatic fever, the symptoms of the disease returning rather promptly after discontinuance of both types of medication. From this salicyl would not appear to be any more specific and curative than quinine and morphine.

Patient 3 (*M. A.*). *Diagnosis*—rheumatic fever. Temperature on admission, 102.3° F. Administered 2¼ grains morphine together with 170 grains of quinine during the first five days, with partial improvement of the condition. The joint pains disappeared so that the patient could easily roll in bed. The temperature fell to normal on the third day and gradually rose, remaining at a level between 99 and 101° for the next two days. On the sixth day of the disease 17.1 gm. (263 grains) of salicyl was administered to "toxicity" owing to the return of pain and swelling in the joints originally involved, fever and general discomfort. The temperature fell promptly to normal on the following day and the patient was free from pain and generally comfortable. This lasted only during the next day. On the eighth day fever, pains, and tenderness in the joints, and general discomfort reappeared and remained unchanged, except for the temperature which showed a tendency to return to the normal, until the patient was made "toxic" again on the tenth day with 200 grains of salicyl. After this, and for the next six days, the temperature tended to remain above normal (moderate fever), but the symptoms of pain and general discomfort disappeared. On the seventeenth day salicyl medication 10 grains every two hours was begun, and maintained until the twenty-first day, or the end of the patient's sojourn in the hospital. His condition remained unchanged, that is, there seemed to be complete relief brought about by the salicyl, a total of 70 gm. (1078 grains) having been administered.

About a month later the patient returned to the hospital with another attack of rheumatic fever which was successfully treated by means of salicyl and prolonged rest in bed.

It may be concluded that partial relief was obtained by the administration of morphine and quinine and salicylate and that this was more complete after the repeated administration of a large quantity of salicyl. However, the condition recurred in its original severity. Therefore, it appears doubtful if salicyl possesses a specific curative property in rheumatism.

Patient 4 (*T. F.*). *Diagnosis*—rheumatic fever. Temperature on admission 101° F. Administered ¼ grain morphine hypodermically, together with 10 grains of phenacetine by mouth every 2 hours for 2½ days, then morphine and quinine in the same dosage for one day. A total dosage of quinine sulphate 130 grains, morphine sulphate 7½ grains, and phenacetine 160 grains, both administered during the first four and one-half days of the disease. During this time there was a temporary (for 2 days) relief from fever and then the temperature gradually rose; some amelioration of discomfort and disappearance of pain in some joints on the second day of treatment, but the pain gradually increased and progressively involved other joints together with increased discomfort. Patient was now made toxic with 20.8 gm. (330 grains) of salicylate. For the next 2 days the temperature fell, ranging from subnormal to normal, and the patient was free from pain and was comfortable. After this the temperature gradually rose and symptoms of pain and discomfort increased. Morphine 1½ grains, together with quinine 60 grains were administered during the next two days without amelioration of pain in the joints and general discomfort; and the temperature remained about normal with small oscillations above and below the normal for 3 days. With the exception of the temperature which tended to remain subnormal, the symptoms persisted in more or less aggravated form for the next 42 days, or until the end of the 51st day of the disease, being relieved only when the patient was made toxic by salicylate, and during this time 8 toxic doses and intermediary salicyl medication, or a total of 1300 grains were administered. The patient received a grand total of 1620 grains of salicylate.

It may be concluded that partial relief was obtained with both nonsalicyl and salicyl medications but the relief appeared to be somewhat more complete with repeated salicyl treatment although it was difficult to discount the psychic element.

Patient 5 (*H. G.*). *Diagnosis*—rheumatic fever. Temperature on admission 104° F. During the first three days of disease 4½ grains of morphine and 180 grains of phenacetine were administered, and on four different days during the next eight days one grain of

morphine and 40 grains of phenacetine were administered, making a total of 5[illegible] grains of morphine and 220 grains of phenacetine during the first eleven days of illness. The temperature returned to normal on the second day of disease, rose to 101.4° on the third, and fell to normal on the fourth day, remaining subnormal from the sixth to the fourteenth days. The original severity of the joint symptoms such as pain, swelling and redness gradually disappeared and on the seventh day the patient felt well enough to get up, but the symptoms gradually reappeared together with a marked rise in temperature on the fourteenth day the pain reappearing in the same (knee) joint, and further medication was necessary. The patient was made "toxic" with 140 grains of salicyl, the temperature fell, and the patient was comfortable during the next two days. However, on the seventeenth day the pain in the joints reappeared together with a slight elevation in temperature. Morphine, ¼ grain, and phenacetine, 10 grains, were administered. The pain in the knees was temporarily relieved. Salicyl to "toxicity" (180 grains) was administered on the twenty-second day, with recovery of pain in the left knee joint, the right knee remaining stiff and painful to the end of the patient's sojourn in the hospital, i. e., the twenty-seventh day.

Prompt though partial and temporary recovery followed nonsalicyl medication in the beginning of the disease. The administration of salicyl gave further relief but no complete recovery.

Patient 6 (*J. D.*). *Diagnosis*—rheumatic fever (relatively mild attack). Temperature on admission, 101.4° F. Administered phenacetine 10 grains together with morphine ¼ grain each day during the first two and on the fourth days; administered a total of phenacetine 30 grains, morphine ¾ grain. During this time, the patient was fairly comfortable although pain in the joints persisted and remained unchanged. The temperature fell to normal after the second dose of the drugs and then returned to 100°, and again fell to 97° on the fourth day, returning to 99.8° on the fifth day. After the fifth day, and to the end of the patient's sojourn in the hospital (end of fourteenth day), the temperature remained subnormal, and all symptoms of the disease disappeared completely, without further medication of any kind. The disappearance of all the symptoms coincided with the fall of temperature on the fifth day, the patient making an uneventful recovery in the next ten days.

In this patient, therefore, complete relief was obtained without salicyl medication.

Patient 7 (*S. R.*). *Diagnosis*—Rheumatic fever. Temperature on admission was 100° F. On the first day 50 grains of phenacetine and 1¼ grains of morphine were administered, with fall of temperature to 97° and complete relief from symptoms of pain in joints and general discomfort for 3 days. On the fourth day, the temperature rose to 100°, and pain in the same joints (left elbow and shoulder) returned. This continued in more or less aggravated form, despite the administration of single daily doses of phenacetine (10 grains) together with morphine (¼ grain) for the next eight days. During this time there were daily changes in temperature ranging from normal in the morning to a moderate fever of 100° in the afternoon. There was no general marked discomfort complained of. A total dosage of 160 grains of phenacetine and 4 grains of morphine had been administered. However, on the eleventh day the patient received a toxic dose of salicylate amounting to 140 grains. The temperature had returned to normal the day before the administration of salicyl and tended to remain subnormal for the next six days. Pain in the joints disappeared and the general condition of the patient improved. On the fifteenth day the patient was discharged completely relieved of symptoms of rheumatic fever.

The symptoms of rheumatic fever were partially though temporarily relieved by the administration of phenacetine and morphine in the beginning of illness, and although the temperature returned to normal before the administration of salicyl was begun, it is seen that more complete relief from the remaining symptoms ensued after salicyl.

Patient 8 (*J. T.*). *Diagnosis*—rheumatic fever. Temperature on admission 100.4° F. Administered 3½ grains of morphine together with 130 grains of phenacetine during the first three days of illness. There was a fall of temperature to 98° on the second day, and remained subnormal with small variations for the next seven days. After the third day the patient remained free from pain and other symptoms for the next seven days. Symptoms of pain, redness, and swelling in joints, general discomfort and fever, returned on the tenth day. The patient was made "toxic" with 300 grains of salicylate, and during the next three days 540 grains of salicyl were administered, or a total of 840 grains without relief of pain and other symptoms in the joints, the temperature, however, remaining

subnormal. In fact, the patient's condition was worse than on admission. The patient now (on the fifteenth day) received 10 grains of antipyrine and remained in bed for the next two days, with the relief of symptoms in some of the joints, but other joints continued to be involved. During the next three days 3 grains of papaverine together with 30 grains of antipyrine were administered. The temperature remained subnormal during the remaining sojourn in the hospital, or the end of the 36th day, and the symptoms of pain and swelling in joints, and general discomfort gradually disappeared, although some stiffness in the joints persisted.

Nonsalicyl medication gave prompt and practically complete relief from the symptoms of rheumatism during the first attack. Salicylate in large doses was ineffective during the second attack, but complete relief ensued following the administration of antipyrine and papaverine. This does not speak favorably for salicylate.

Patient 9 (*L. S.*). *Diagnosis*—rheumatic fever. Temperature on admission 104.6° F. For two days previously had received unknown quantity of salicyl, became "toxic," but without relief of joint symptoms and fever. Patient was brought into hospital on last day of salicyl treatment, his condition being more aggravated. That night patient received 2 grains of papaverine together with 20 grains of quinine. On the following day, the temperature fell to 97°, rose to 100° on the second day, and again to 100.8° on the third day, and then gradually fell to normal on the fifth day, and remained unchanged till the end of the eighth day, when he was discharged. Following the administration of papaverine and quinine the patient was more comfortable and the symptoms of swelling, pain, and redness in the joints gradually disappeared, so that by the end of the fourth day the patient had obtained complete relief from all symptoms of the disease, and remained so until the date of his discharge.

No relief in this patient was obtained by salicyl medication; complete relief followed the administration of two doses of papaverine and quinine. It is possible that the patient would have recovered without any medication after the salicyl period.

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CLINICAL MANIFESTATIONS OF EMPYEMA*

By Captain Warren T. Vaughan, M.R.C., U. S. Army.†

WERE the physical signs in all cases of empyema the same, the problem of recognition and of proper treatment would be comparatively simple. But just as the proper indications for operation may vary with each case, so in no two cases may the evidence of pleural pus be said to be identical. Nevertheless, for convenience, and in an attempt to clarify the problem, we have classified the various empyema cases as seen on the medical service into certain groups, the individual members of which present in a general way the same history, course and physical findings. The following nomenclature has been chosen as being descriptive of either the clinical or the anatomical manifestations in the different groups:

I. Primary empyema.
II. Precocious empyema.
III. Cryptic empyema.
IV. Massive empyema.
V. Suppurative polyserositis.
VI. Interlobar empyema.
VII. Juxtamediastinal pus.
VIII. Polylocular empyema.
IX. Latent empyema.

I. PRIMARY EMPYEMA

This group comprises a few patients who have been admitted suffering from an illness of but short duration, the onset of which has been sudden with chills, fever, and pleural pain, and on whom the diagnosis of lobar pneumonia has usually been previously made. The physical findings on admission may be those of a large fluid accumulation, dullness to flatness with absent tactile fremitus, and diminished or absent breath and voice sounds, or the voice sounds may be fairly well transmitted. Fluid is at once suspected and thoracentesis confirms the diagnosis. In some of these cases it is difficult to state whether the empyema is primary or whether it is secondary to an intrapulmonary condition. We have found the character of the sputum to be of material aid in thus distinguishing a primary empyema. In it there is neither the tenacious sputum of lobar consolidation nor is there the easily raised muco-pus of bronchopneumonia. Cough may be present and urgent but it is quite nonproductive.

We have had two cases of primary empyema in our operated series, one of whom gave a history of recent measles infection while the other did not. Of how great importance the measles could be in predisposing to involvement of

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the pleural cavity can be but a matter of conjecture. In this camp the pneumococcus has been the organism found in the pleural exudate.

In addition we have had two cases of primary serofibrinous pleurisy in whom the chest fluid contained pneumococci. Both patients were aspirated repeatedly and the first recovered without operation while the second finally developed frank pus and was drained surgically.

II. PRECOCIOUS EMPYEMA

It is a common saying that if the temperature in a case of lobar pneumonia remains up after the seventh to the tenth day of the disease it is well to suspect a complicating empyema. It is indeed true in our experience that following frank lobar penumonia, true pus did not appear in the pleural cavity in the majority of cases until after the time for crisis. Of twenty-five cases in which the date of empyema diagnosis is definite, only one had the complication previous to the seventh day, and that on the second day. Four cases occurred on the tenth day, three on the twelfth and one or two occurred on other days from the seventh as late as the thirty-seventh.

But it would be negligence to wait until the seventh day before beginning the search for empyema. The majority of the cases develop, first, a serofibrinous pleurisy containing organisms and, later, pus. Although the latter has occurred in lobar pneumonia after the seventh day, the former in two-thirds of the cases was proved by thoracentesis to be present previous to the seventh day. Upon the early recognition and repeated aspiration of this clear fluid frequently depends the possibility of avoiding subsequent rib resection.

Amongst the postinfluenzal group of pneumonias which occurred during the spring frank pus developed more rapidly than in the primary lobar pneumonias. Of seven such cases five developed pus previous to the sixth day.

To summarize, we have had four cases of precocious empyema following lobar pneumonia, one on the first day, two on the second and one on the third. Two more are noted among the postinfluenzal cases as occurring on the fifth day. In all other cases in which the information is exact, pus did not occur until after the seventh day. Among the bronchopneumonias also precocious empyema is the exception. The majority of cases were discovered after the ninth day.

III. CRYPTIC EMPYEMA

One feature of the empyema problem that has elicited comment from several camps is the apparent fact that our previous teachings concerning the physical indications of pleural fluid are erroneous as regards the postbronchopneumonia empyemata. It is true that most of the cases occurring during the severe bronchopneumonia epidemic did not show typical signs of fluid. But as we have become better acquainted with this type of chest we have concluded, not that the old signs of fluid are at fault, but that their enumeration must be modified by certain exceptions and amplifications. It is difficult and in occasional instances nearly impossible to demonstrate fluid from the physical findings in the bronchopneumonias that we have had in camp, but that it can be done is indicated by the fact that, since the latter part of December, 1917, scarcely a

case with pleural fluid has gone to autopsy undiagnosed, even though the amount be small.

Perhaps the most disturbing finding over fluid is the presence of rales. Coarse, moist, sticky rales may be heard over a fluid which nearly half fills one side of the chest. It is never safe to decide, because rales are present and seem close to the ear, that fluid is absent. We do not recall, however, having heard the typical fine crepitations of pneumonic consolidation over fluid.

Among the signs indicative of fluid in bronchopneumonia there are two of paramount importance. First of these should be mentioned diminished or absent breath sounds. Where breath sounds are distant and even though dullness be but moderate and rales be present, fluid should be suspected. Flatness to percussion, best determined by comparison with percussion over the deltoid muscle, is a frequent indication of fluid in bronchopneumonia. Also in cases showing dullness without true flatness and with distant breath sounds, fluid is to be suspected.

The presence or absence of a Grocco's paravertebral triangle or of transmitted tactile fremitus have been only of confirmatory value. Displacement of the heart borders, the apex impulse or the point of maximum intensity of the heart sounds is frequently a valuable diagnostic aid. The patient's general condition is of aid in lobar pneumonia but in bronchopneumonia, the sweating, cyanosis and wide diurnal temperature excursions are nearly as frequent where empyema is absent as when it is present.

In choosing the point for thoracentesis one is governed, at times, by the flatness of the percussion note and, at times, by the diminution of the breathing and of the whispered voice. It frequently is necessary to insert the needle to a considerable distance before fluid is reached. Another surprising observation is the relatively large amount of fluid that may be obtained at operation, even though two or three previous needlings, within a rather limited area, were necessary before it could be found. Provided there is strong evidence that fluid is present, one should not rest content with a single nonproductive needling. Thoracentesis should be persisted in until there is no longer any uncertainty. Usually two, or at the most three, needlings will definitely settle the question.

The frequent accumulation of encapsulated fluid in bronchopneumonia would appear to be the explanation for the anomalous signs in empyema. Congestion and compression of the surrounding pulmonary tissues accounts in part, at least, for the presence of rales. In lobar pneumonia, cryptic empyema is less frequently present and the classical signs of fluid are in evidence.

IV. MASSIVE EMPYEMA

This well-known condition has occurred in a small number of our series. More frequently the pyothorax is walled off by adhesions and limited in its extent. In the larger effusions and in those loculated effusions which occur in the region of the left axilla, displacement of the heart and Grocco's sign have been of assistance. Information obtained from examination for tactile fremitus has varied directly with the size of the fluid accumulation, fremitus being characteristically absent over the massive empyemata.

V. SUPPURATIVE POLYSEROSITIS

This condition deserves mention chiefly because of its comparative infrequency. We have chosen this name to designate those cases following lobar, or more particularly bronchopneumonia, in which at autopsy there is found to be present a bilateral empyema, a purulent pericarditis, and a general peritonitis. In our series we have had but two cases showing all of these findings but have had three or four additional in whom peritonitis occurred as a complication to pneumonia, and in one of these there was also a unilateral empyema. In the case of two patients who were first operated for appendicitis, subsequently developed pneumonia and finally terminated with peritonitis, the pneumococcus was found to be the organism invading the peritoneum. We have had two cases with bilateral empyema and suppurative pericarditis as instances of a form of suppurative polyserositis.

The problem as to whether spread to other serous cavities is metastatic or by direct invasion through the diaphragm or pericardium is unsettled. There are those who claim that pericarditis complicating pneumonia results from direct spread, but the occurrence of pericarditis or peritonitis in pneumonia cases without empyema seems scarcely explainable by such an hypothesis.

Pneumococcus peritonitis, as it has occurred in this camp, is evidenced by few symptoms. There may be some distention and but moderate rigidity and tenderness. Or the symptoms may be very definite. At autopsy one finds small collections of sweet-smelling, greenish-yellow pus lying between the folds of the intestines and settled in the dependent fossae. The distribution is usually throughout the entire peritoneum.

VI. INTERLOBAR EMPYEMA

This has been observed in a few instances at autopsy. Among those who have survived, its possible presence is frequently indicated first, by the x-ray, second, by the fact that signs of fluid are not definite, and third, by the fact that it frequently is necessary to insert the needle to a considerable depth before fluid may be obtained. We have had three typical cases of right interlobar empyema in which fluid could be obtained only from the region covered by the midscapula when in its normal position and then, only after the needle had been inserted to its full extent. In these cases the most useful physical sign was flatness to percussion after the scapula had been moved well out of the way. The x-ray gives valuable assistance in these cases.

VII. JUXTAMEDIASTINAL PUS

So frequent have been our cases of loculated empyema between the visceral pleura and pericardium or upper mediastinum, that we have included them in our classification as a distinct group. Particularly has this condition been found to be present at autopsy. Among the earlier cases of our series there was one patient who had developed a postpneumonia empyema and who had been drained surgically. He had been doing fairly well and the drainage had become quite scant when, unexpectedly, his condition became worse, and

in spite of attempts to locate more pus he died. At autopsy the drainage was found to be quite complete in the cavity drained but between the lung and the upper mediastinum there was a considerable walled off accumulation of pure pus. We have also been able to find this condition during life and, through appropriate treatment, to cure the patient. Here, again, the x-ray is of inestimable value.

Instances have been found at autopsy of suppurative mediastinitis. We have one patient at present on the ward who shows the classical signs of this condition, substernal pain, increase in mediastinal dullness and in mediastinal shadow by x-ray, unequal pupils and pulses, and the constitutional signs of pus. More recent x-rays show evidence of encapsulation adjacent to the upper mediastinum and it is possible that this case is not one of suppurative mediastinitis but juxta-mediastinal empyema. He is progressing favorably.

VIII. POLYLOCULAR EMPYEMA

A condition of considerable importance is the presence in the same chest of more than one loculated fluid collection. We have had two patients in whom we were able to obtain clear serous fluid from one area and pus from another. The case cited under juxtamediastinal pus is another example. One fluid collection may be parietal while the second is interlobar and under these circumstances the latter is especially liable to be missed. Associated with the condition of polylocular empyema should be mentioned an occasional finding in drainage cases where the temperature remains elevated although the discharge has become scanty. This is frequently due to walled-off pus which the tube no longer reaches. In all of the above conditions the x-ray gives considerable aid.

IX. LATENT EMPYEMA

In decided contrast to those individuals in bronchopneumonia whose condition rapidly becomes critical, with accumulation of serofibrino-purulent fluid in the pleural cavity and who die even before the fluid has opportunity to become real pus, are occasional cases who may carry about, without reaction, a chest nearly full of pus. One patient in our earlier series carried about with him an empyema which had escaped detection until the physical examination preliminary to discharge. Pus was found on the thirty-seventh day after his pneumonia and after his temperature had remained normal for fourteen days. After removal of the pus, the patient was discharged well.

USEFULNESS OF THE X-RAY

The x-ray has two fields of usefulness which easily render its aid indispensable. The first of these is the possibility of thus discovering interlobar empyema, juxtamediastinal pus and polylocular fluid. The second and equally important phase of the x-ray work is in the examination of convalescent empyema patients who have been up and about for some time, who do not regain strength as they should do and who occasionally have a mild temperature elevation. In these, radiograms at times demonstrate a small pocket of sacculated

pus sometimes contained together with air in a thick walled cavity. Aspiration without operation, provided the fluid is small in amount, sometimes produces satisfactory results.

MEDICAL "FOLLOW-UP" TREATMENT

We would emphasize the importance of medical "follow-up" work on post-operative cases. It has been the custom in this hospital for the man who has general supervision of the pneumonia cases to devote a portion of his time to examination of empyema cases on the surgical wards. He makes daily examinations of acutely ill patients and notes his findings on the clinical record, together with whatever recommendations he considers advisable. Search is made for evidences of retained pus and for complications, particularly pericarditis, peritonitis and beginning fluid accumulation on the well side of the chest. In a few patients signs of considerable fluid remained even though the drainage tube appeared to be functioning properly. Following the recommendations of the medical man adhesions were broken up and the walled-off pus was evacuated. The presence of a drainage tube is no counterindication to the use of the exploratory needle in cases where there is a question as to the persistence of pus.

COCAINE POISONING. REPORT OF A CASE WITH NECROPSY*

By Ellis Kellert, M.D., Albany, N. Y.

SINCE the advent of local anesthesia, practically all who have had extensive experience with the various preparations have at times encountered instances of acute poisoning and occasionally death immediately after their use. Fatal cases are not exceedingly rare and it is certain that many deaths due to the anesthetic are not so recorded. Cocaine hydrochloride as used clinically appears to be particularly toxic, since symptoms of poisoning occur quite frequently even after the use of small quantities. There are, however, considering the widespread use of cocaine, but comparatively few fatal cases reported. Witthaus and Becker state that up to 1911 only sixty-seven deaths from cocaine have been reported and from 1911 to date only seven reports of fatal cases have been added. In a rather extensive pathologic experience the case herein recorded is the first instance in which a necropsy has been secured by us. Because of the rarity of such examinations and furthermore since the Therapeutic Research Committee of the Council on Pharmacy and Chemistry of the American Medical Association have particularly requested all available data, this accidental death following the use of cocaine is described although the clinical history is rather brief.

Clinical History.—The patient, a man, forty-six years of age, an agent, complained of pain in the lower right quadrant of the abdomen. On the preceding day he suffered from "colic" and vomited three times. Temperature 100° F., pulse 96, respirations 24. Patient entered the hospital and the appendix was removed.

That night at 12 P.M. the resident physician attempted twice to catheterize the patient but without success. Slight bleeding followed each attempt. About two hours later, "three drams of a 4 per cent cocaine solution were injected into the urethra. The patient immediately had a convulsion and died."

Necropsy.—Twelve hours postmortem. Body length 180 cm.

The body is that of a well-built, well-developed white male adult. Rigor mortis is present. There is very slight postmortem lividity in the dependent portions. There is no edema of the extremities and no general glandular enlargement. The pupils are midwide and equal. To the right of the umbilicus is a recent appendectomy wound.

Peritoneal Cavity.—The surfaces are normally smooth, moist and glistening. The stomach is slightly dilated. The appendix has been removed and the site of operation appears clean, but blood stained. A small quantity of fluid blood is found in the right iliac fossa. The adjacent coils of intestine are slightly injected and adherent.

Pleural Cavities.—The surfaces appear negative. A few adhesions are found about the upper lobes on each side. An occasional area of brownish pigmentation is also present.

Lungs.—The right lung is somewhat voluminous and the left is collapsed. Both show moderate congestion but crepitation is present except in the lower lobes which are dark red on section and filled with fluid blood. Dissection of the large vessels shows no thrombi or emboli.

Heart.—It weighs 320 grams. All cavities appear to be dilated, particularly the right side, where a large quantity of fluid blood is found. The blood is dark red in color and only a few small clots are present. The pericardium is negative. The endocardium and valves also appear normal. The coronary arteries are patent throughout and no narrowing of the lumen is found. The myocardium is dull red and unusually soft and flabby. The ventricular walls are thinner than normal, the left being 1.5 cm.

*From the Bender Hygienic Laboratory, Albany, N. Y.

in thickness. Nothing unusual is found on section. The pulmonary artery is opened in situ and no thrombi or clots of any description are found.

Gastrointestinal Tract.—The stomach is slightly dilated, but not otherwise abnormal. The mucosa appears negative. The small and large intestines also appear normal. There is no enlargement of the mesenteric lymph nodes.

Pancreas.—It is not remarkable.

Spleen.—Weight 175 grams. It is dull red in color and appears normal.

Liver.—Weight 1850 grams. It is dark red in color. The surface is friable and the hepatic lobules are very distinct. The gall-bladder and bile passages are normal.

Kidneys.—Combined weight 250 grams. They appear small and are dark red in color. The capsule strips readily, leaving a smooth surface. Cut surface is distinctly injected and fluid blood escapes. The pelves and ureters are negative. The bladder is greatly distended, containing approximately one liter of bloody urine in which a few small clots of blood are found.

Genitalia.—The prostate is not enlarged. The prostatic urethra appears normal. On opening the entire length of the urethra, the surface appears smooth and normal. No areas of ulceration are found. The lacunæ are prominent. The testicles are normal.

Aorta.—It is normal throughout.

Brain.—Weight 1400 grams. The dura and inner surface of the calvarium are normal. The pia-arachnoid is distinctly edematous and injected. Serial sections are made and nothing pathologic found.

Anatomical Diagnoses.—Acute dilatation of heart, acute congestion of liver, kidneys, spleen and lungs; edema of cerebral meninges, chronic pleuritis, absence of appendix (operation).

Microscopic Examination.—

Heart.—There is marked "fragmentation" of the muscle fibers. The capillaries are not unusually distended, but an occasional area of interstitial hemorrhage is found. Pigment is not increased and the nuclei appear normal. Sections show the right ventricular wall to be unusually thin, otherwise negative. There is no increased amount of fat present.

Liver.—There are no marked alterations. The sinusoids adjacent to Glisson's capsule are distended with blood. Elsewhere they are somewhat less congested.

Spleen.—Great engorgement, with interstitial hemorrhage. The smaller vessels show hyalin changes in the intima.

Pancreas.—Not remarkable.

Kidney.—The vessels are greatly distended with blood. Moderate degenerative changes of the tubular epithelium present. The glomeruli are congested. All the tubules adjacent to the capsule are dilated and contain a fibrinous deposit. Similar deposits are found in the glomeruli in this region.

Bladder.—Congestion and edema. Separation of the muscle bundles between which are found a fibrinous deposit and occasional extravasation of blood.

Intestine.—The ileum contains an excessive amount of mucus. Numerous polynuclear leucocytes are found beneath the serosa, in the mesenteric fat and between the muscle bundles.

Cerebrum.—Edema of the cortex. Meninges show marked distention of the vessels, slight cellular infiltration and areas of great pial thickening. The molecular zone presents a rarefied or vacuolated appearance and the nerve cells found within this zone stain poorly as though due to acute degenerative changes.

Cerebellum.—The vessels of the meninges are congested. Slight periadventitial lymphocytosis.

Prostate.—A few areas of lymphocytic infiltration present.

Seminal Vesicles.—Muscular hypertrophy. Very few spermatozoa present. Many of the epithelial cells contain a brownish pigment.

Urine.—Numerous leucocytes, erythrocytes, tailed epithelial cells, spermatozoa and oil droplets are present.

Chemical examination of the urine from the bladder by Doctor Arthur Knudson is negative for cocaine.

The symptoms and death occurring so quickly late at night did not make possible clinical observations other than these already noted. On subsequent inquiry, it was learned that the cocaine used was in the form of a 4 per cent

stock solution and comparatively fresh. The resident physician stated that about three drams were used and this would correspond approximately to 0.50 gram of cocaine hydrochloride. The lethal dose is variably estimated, but generally considered to be less than 1.000 gm. In nearly all urethral cases reported, less than 1 gram has caused death and it is very likely that a much smaller quantity produced the actual poisoning.

Since the publication of Witthaus and Becker but few cases have been recorded, although a number of instances are related where symptoms of poisoning ensued. There is little doubt that many deaths have occurred either accidentally or in the case of cocaine habitues from over dosage. In the cases reported by Witthaus and Becker the dose is stated in but twenty-five and of seven cases recorded since 1911 we find the quantity stated in four. In addition to the fatal cases following the injection of cocaine, many others are reported where the simple application of a 4 per cent solution to burns or ulcers or in the form of a spray in the nose caused death.

The onset of symptoms may be immediate or delayed for several hours. Death usually occurs promptly, but is less likely to happen with an increasing interval of time and rarely takes place after three hours. Excitement and convulsions followed by collapse are the chief symptoms and death appears to be due to cessation of respiration or of heart action.

Nothing characteristic is found at postmortem examination. In our case, dilatation of the heart, acute congestion of the organs and edema of the meninges were the chief changes noted and correspond to the results obtained in previous necropsies. The interstitial hemorrhage noted in the heart and bladder wall may be due to the intense congestion, or to a preceding violent heart action with vascular contraction and increased blood pressure. Direct action on the heart muscle is not unlikely, because in many of the rapidly fatal cases the drug undoubtedly obtained immediate access to the circulation either by application to raw surfaces or by urethral injection following attempts at catheterization when minute abrasions of the mucosa may have been produced, or by subcutaneous injection with the entry of the drug into a small vessel. The changes in the central nervous system may have been brought about by the preceding anesthesia.

The rapidity of action is noteworthy. Many of the accidental deaths encountered by physicians have followed intraurethral injections and usually there has been a history of slight bleeding. This would seem to indicate that the injured mucosa permitted the rapid absorption of comparatively large quantities of cocaine, with immediate action on the heart muscle and respiratory centre. When the drug is slowly absorbed, toxic symptoms may ensue but usually without fatal result. It has been noted by Sollmann that in the urethra of male dogs, larger quantities of local anesthetics are more rapidly absorbed and that the rapidity of absorption is most rapid during the first ten minutes. In a recent investigation on the comparative absorptive power for drugs of the urethra, Macht noted that urethra possesses greater absorptive power than the bladder, and that the posterior urethra absorbs more rapidly than the anterior urethra. He attributes this fact in part to the presence of glands, but in a previous paper,

Doctor Macht also shows that rapid absorption of cocaine may occur from such a surface as the vaginal mucosa where no glands are present.

The anesthetics often substituted for cocaine may also produce toxic symptoms. Thus Jacobs reports two cases of poisoning from the use of alypin in the urethra. In each instance 2 drams of a 2 per cent solution was used and slight bleeding was noted. In a few minutes after the injection there occurred violent convulsions, cyanosis, and weak pulse, but recovery followed. Jacobs concluded that more rapid absorption took place from a traumatized surface.

The variable quantity of cocaine stated as the cause of death would seem to indicate that some individuals are more susceptible than others. A method to detect this increased susceptibility would be highly valuable but does not appear possible at this time, since the true action of cocaine is not known (Kuroda) other than its paralyzing action on sensory end organs. Since characteristic symptoms are produced quite promptly, however, it might not be impractical to make a preliminary injection of a small dose and watch for signs of poisoning. This may be tried particularly in the urethral cases which in medical practice appear to have produced the greatest number of deaths.

In the fatal cases death occurs so promptly that little can be done to counteract the action of the drug. It has been suggested that alcohol or hyoscin hydrobromid be administered just prior to the injection of cocaine in order to prevent symptoms of poisoning. After symptoms have appeared, rapidly acting cardiac and respiratory stimulants are indicated.

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ACUTE ADRENAL INSUFFICIENCY*

By William Boyd, M.D., Winnipeg, Canada.

IT is now over a century since Addison first described the condition to which his name has been attached, a condition characterized by profound asthenia, low blood pressure, gastrointestinal disturbance, and a remarkable pigmentation of the skin and certain of the mucous membranes, associated generally with tuberculous destruction of both adrenal bodies. In the years which have elapsed a vast amount of work has been done upon the physiology of the adrenals, and one brilliant discovery has been made, but it can not truthfully be said that a single ray of light has been shed on the nature of the relationship which exists between disease of the adrenals and the symptom-complex of Addison's disease. It need cause no surprise, therefore, that the extraordinary condition to which the name acute adrenal insufficiency has been given should remain a complete mystery, for the function of the adrenals is still largely unknown.

Part of this ignorance is perhaps due to the fact that too much stress has been laid on the methods of the physiologic laboratory, with the result that the possibilities of morbid anatomy as an aid in elucidating these problems have been belittled or overlooked. As one of the leaders of physiologic thought has justly said: "The world of pathologic phenomena is nothing but an endless series of the most different and unusual combinations of physical occurrences which never make their appearances in the normal course of life. It is a series of physiologic experiments which nature and life institute, with such an interlinking of events as could never enter into the mind of the present-day physiologist, and which could scarcely be called into existence by means of the technical resources at our command. Clinical observation will consequently always remain a rich mine of physiologic facts."

The dual nature of the adrenals is well recognized. As in the case of the pituitary the gland consists of two parts which are perfectly distinct in development, in structure, and almost certainly in function. The cortex is developed from the mesoderm, the medulla, in conjunction with the sympathetic system, from the neural ectoderm. The cortex consists of columns of cells loaded with a doubly refracting lipoid material, an ester of cholesterin, which varies in amount in different physiologic and pathologic conditions. The medulla is part of the system of chromophil tissues, and contains the substance adrenalin.

The analogy to the pituitary is worth noting. In the pituitary there is a part—the pars posterior—which is composed of inert-looking, nonglandular material, and yet the extract prepared from it is one of the most powerful physiologic substances with which we are acquainted. The glandular anterior portion, the extract of which produces no remarkable effects, is, however, the part which is probably essential to life. In the adrenal the medulla produces an equally active substance, and the more glandular cortex appears to be correspondingly inert, but here again evidence is slowly accumulating which seems to indicate that the apparently inert part is the one vital to the individual.

*From the Department of Pathology of the University of Manitoba.

It is only in the mammal that these widely differing structures are found in the relation of cortex and medulla. In birds they occur as intermingling columns, and in elasmobranch fishes they are entirely distinct organs, the cortex being represented by an elongated interrenal body lying between the caudal ends of the kidneys, and the medulla by a succession of paired chromophil bodies. It may be, however, that the union of the two parts in the mammal may have for its object the functioning of the two parts as one organ. Of this we have no knowledge.

The discovery by Oliver and Schäfer that the medulla contains a substance of remarkable physiologic activity which acts upon the structures supplied by the sympathetic system, together with the therapeutic applications of this discovery, has served to focus attention, perhaps unduly, on this constituent of the gland, with the result that the cortex has been largely neglected.

At present we know nothing of the function of the cortex. It has been suggested that it exercises a control over sexual development, as the anterior lobe of the pituitary undoubtedly does. It is true that certain tumors of the cortex in children are associated with a remarkable precocity in the development of the sexual organs, and that similar tumors in elderly women may be accompanied by a development of male characteristics. It is possible also that the cortex may be intimately associated with the metabolism of lipoids, especially cholesterin. The fact remains, however, that we have no real knowledge on the subject.

Nor is there even agreement as to whether the cortex is essential to life. Some element of the gland certainly is necessary. Extirpation of one adrenal in the animal produces no effect, but removal of both adrenals is followed by death, generally in from two to four days. Attempts to remove the cortex alone or the medulla alone have failed to throw conclusive light on the subject, owing to the technical difficulties of the operation. The general view at present held is that it is to the loss of the adrenalin-producing substance that the fatal effect of complete adrenalectomy must be attributed. And yet removal by Biedl of the interrenal body, that is the cortex, in cartilaginous fishes, in which separation of the two systems is unusually well marked, was followed by asthenia and death.

This important question is therefore still undecided, and as the methods of experimental physiology have failed in this instance, it remains to be seen whether morbid anatomy can throw any light on the subject.

The relationship of the syndrome of Addison's disease to disease of the adrenals is well established, but of the nature of this relationship we have little real understanding, nor can it be said that recent physiologic research has furthered to any appreciable extent this understanding. It is impossible to reproduce the symptoms of Addison's disease in animals. The low blood pressure and lack of vasomotor tone are no doubt due to deficiency in adrenalin, but the cause of the muscular asthenia, the pigmentation, and the gastrointestinal disorder is still a matter for conjecture.

Further complicating the problem is the fact that cases of Addison's disease may occur with apparently healthy adrenals. In such cases there is often some degeneration of the chromophil tissue in relation to the abdominal sympathetic, and the great sympathetic ganglia may show pathologic changes of va-

rious kinds. Moreover there may be most extensive destruction of the adrenals without any symptoms of Addison's disease. An endeavor is usually made to explain away such anomalies by presupposing the presence of accessory adrenals, but if these bodies—which at best are minute in comparison with the adrenal itself—are as frequently present as has been claimed, it is remarkable that they do not come to the rescue in cases of typical Addison's disease.

The onset of the syndrome described by Addison is gradual. Adrenal insufficiency, however, may be acute instead of chronic in type, with a very different resulting clinical picture. The condition is named acute adrenal insufficiency, but that must not be taken to imply that it bears any definite relation to the symptoms of Addison's disease. It owes its name solely to the fact that the only constant lesion found is profound destruction of both adrenal glands. Of such a condition the following case is a striking example.

The patient, a soldier, thirty-eight years of age, was in Winnipeg on a few days' leave of absence. Up to the time of his leave he was performing the more or less arduous duties of a military training camp. It may therefore be assumed that he displayed no marked myasthenia nor other grave symptoms of organic disease. Early one morning he was found in a semiconscious condition in his room. A few hours later he was admitted to the Winnipeg General Hospital under the care of Doctor J. R. Davidson. By that time he was sinking into a state of coma. The picture was one suggestive of cerebral hemorrhage. The limbs were rigid, the reflexes gone, and the pupils distinctly dilated. The face and hands were cyanosed. The temperature was 99° F. Urine was drawn off and found to be normal. Lumbar puncture was done, but the cerebrospinal fluid showed no change and gave a negative Wassermann reaction. The patient died two and a half hours after admission. The clinical course was thus apoplectiform in type.

The autopsy was performed within two hours of death. Old adhesions were present over the liver, spleen, and mesocolon. Both pleural cavities were obliterated by old adhesions. There were fibrous nodules at the apices of both lungs, and a tuberculous cavity the size of a hazel nut in the apex of the right lung. The heart and kidneys were normal. The meningeal vessels were injected, and the cerebrospinal fluid somewhat increased in amount, but the brain showed absolutely no abnormality. The stomach contents when examined later showed no trace of poison.

The only organs exhibiting any marked pathologic change were the adrenals. These were almost entirely destroyed, and converted into structureless, amorphous, yellowish masses, firm in texture, and considerably larger than the original glands. On the right side no trace of adrenal tissue, either cortex or medulla, could be found. On the left a narrow strip of adrenal not more than 2 mm. in width was present at one point. This consisted entirely of cortex, the cells of which contained a lipoid substance which stained red with Scharlach R, but which was not anisotropic. The remainder of the gland consisted of areas of necrosis surrounded by the endothelial and giant cells characteristic of tuberculosis. No trace of medullary substance remained. Attached to the caseous mass was a small nodule which showed the microscopic structure of a sympa-

thetic ganglion. The nerve cells and fibres of this ganglion, stained by various methods, showed no abnormality, but there appeared to be some increase of fibrous tissue.

This case is worthy of study from various points of view. It appears effectually to dispose of the theory that the medulla of the adrenal is essential to life. The entire medulla must have been completely destroyed for a considerable length of time, and yet the patient was in sufficient physical vigor to engage in the full duties of a military camp. Hypertrophy of accessory chromophil substance may be invoked, but this does not invalidate the statement as it applies to the adrenal medulla.

The persistence of a small amount of cortical tissue on the left side certainly suggests that this is the part of the gland which is necessary for the maintenance of life, but that when it is reduced to a minimum the end may come with startling suddenness. It would appear that under some conditions extensive destruction of the cortex may occur without the production of manifest symptoms, owing to the compensatory action of that which remains. When the limit of that compensation is reached, however, the picture of acute adrenal insufficiency makes its appearance.

The case must certainly be classed as one of acute insufficiency of the adrenals. Of this condition four types have been described, chiefly by French authors.

1. The acute abdominal form characterized by severe epigastric pain, lumbar tenderness, vomiting, and profound shock. The clinical picture closely resembles that of acute hemorrhagic pancreatitis.

2. The cerebral form in which convulsions or the rapid onset of coma are the chief features.

3. The asthenic form marked by a rapid and profound asthenia terminating fatally in a few days.

4. A form in which sudden death occurs without premonitory symptoms, and in which the only lesion revealed by autopsy is complete destruction of the adrenals.

In the majority of the cases described in the literature the pathologic finding has been a sudden vascular lesion of the adrenals, either in the nature of a hemorrhage destroying the glands, or a thrombosis of the adrenal vessels. Thus Lavenson describes a case of the abdominal type in which there was thrombosis of both adrenal veins together with acute hemorrhagic necrosis of the glands. It seems probable that all of the abdominal type of cases are of this nature.

The cerebral cases may also be due to an acute hemorrhagic lesion, as in that of Laignel-Lavastine, where a man of thirty-six years, apparently in good health, fell unconscious and died in coma twelve hours later. Arnaud, however, describes a case with an almost identical clinical history, save that the patient lived for forty-eight hours, in which there was no recent lesion, but almost complete replacement of the adrenals by old hematomata and organizing hemorrhagic foci. Janowski and Stursberg also record cases of acute adrenal in-

sufficiency in which the lesion was of a chronic, probably a tuberculous, nature. In this class the present case must also be included.

To explain the relation between the pathologic changes in the adrenals and the extraordinary and dramatic clinical course of the case is beyond our powers. Such a failure, however, will at least serve the useful purpose of recalling to our minds the fact that there are still more things to be learned about the adrenals than are contained in our philosophy. The detailed study of adrenalin has led many to think that we understand the function of these bodies. In reality we are only just beginning to realize our ignorance.

Why such a case should display none of the usual symptoms of Addison's disease we do not know. To appeal to the comparatively unaltered abdominal sympathetic or to hypothetical accessory cortical adrenals is merely to hang a dark cloak over our ignorance. Nor do we yet know the function of the adrenal cortex. Theories unsupported by sufficient evidence mislead by creating a false impression of knowledge, and those which attribute to the adrenal cortex antitoxic and internal secretory functions certainly appear to fall into that category. We see that it is probably essential to life. Let us go no further until evidence has been accumulated which is worthy of the name. Only thus can sure progress be made, and in such progress physiology and morbid anatomy should walk hand in hand.

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LABORATORY METHODS

A CONVENIENT DILUTION CHART OF USE IN SEROLOGIC AND OTHER TESTS IN WHICH VARYING QUANTITIES OF REAGENTS ARE EMPLOYED*

By Loren B. Taber, Berkeley, Cal.

DURING the present international emergency, laboratories are finding themselves divested of technicians while the volume of work increases. The author has been under the necessity of training relatively unskilled helpers possessing only a high school education into making routine serologic tests, and has found that although in selected workers accuracy of technic has been acquired with relative ease, ability to figure dilution tables has been, as a rule, entirely lacking. The situation has been complicated by the fact that when standard serum controls are made, one is usually compelled to use the smallest possible quantities in order to conserve supplies.

In a laboratory in which large numbers of tests are made upon perhaps a dozen different sera requiring widely divergent dilutions, the figuring of each table by the one in general charge of the work is unnecessarily time-consuming. In such a contingency the accompanying chart has proved itself of decided value.

ROUTINE USE OF CHART

Certain values in routine tests are fixed and known to the assistant: total volume of serum-saline-antigen mixture per tube (D); fractional volume of serum mixture in one tube of serum-saline-antigen (E); volume of serum mixture in one tube of serum-saline-antigen (F). The one who lays out the work merely fills in the values for the final dilutions of serum in the finished test, and indicates the antigens to be used, together with the number of tubes of each antigen to be tested at each dilution. The assistant is then able to calculate independently the remainder of the values.

A SERUM DILUTION TABLE FOR A SIMPLE AGGLUTINATION TEST

As a practical example, let us consider an agglutination test (see Chart I) in which four dilutions of serum ,1/100, 1/200, 1/400, and 1/800, and twenty antigens are used. The customary total volume of serum-saline-antigen in one tube (D) mixture is 1 mil; the fractional volume of *serum mixture* in one tube of serum-saline-antigen (E) is 1/2; the volume of serum mixture in one tube of serum-saline-antigen (F) is therefore 0.5 mil. The values are now complete through F.

It is not necessary to calculate G as this value is not used in the final formulas.

*From the Serum Department, Cutter Laboratories, Berkeley, Cal.

The total volumes of the serum mixtures at the different dilutions (H) are found by multiplying the number of tubes at each dilution (C) by the volume for each tube (F). $C \times F = 20 \times 0.5$ mil $= 10$ mils.

For the last dilution, the total volume needed will be only that mixed with the antigens plus a minimum amount (1 mil) for the wetting of glassware. There $I^{IV} = 0$, and $J = H$ mils $+ 1$ mil $= 10$ mils $+ 1$ mil $= 11$ mils.

The volume of *serum* needed for each dilution (K) need be calculated only for column I, as in the final formulas for the following values it does not occur.

The calculation of the amounts of serum dilution and of saline to be mixed now proceeds as follows:

Serum dilution $H^{IV} \rightarrow J^{IV} \rightarrow L^{IV} \rightarrow I^{III} \rightarrow J^{III} \rightarrow L^{III} \rightarrow I^{II} \rightarrow J^{II} \rightarrow L^{II} \rightarrow I^{I} \rightarrow J^{I} \rightarrow K^{I}$.

Saline.—As the chart indicates, the amount of saline to be used in each flask (M) is found by simply subtracting the amount of the previous serum mixture to be used (L) from the total volume desired (J).

Chart I

A Serum Dilution Table for a Simple Agglutination Test

(A convenient table of use in making dilutions with minimum quantities of serum)

A	Number of serum dilution flask	I	II	III	IV
B	Final dilution of serum in serum-saline-antigen mixture	$\frac{1}{100}$	$\frac{1}{200}$	$\frac{1}{400}$	$\frac{1}{800}$
C	Number of test tubes at each dilution	20	20	20	20
D	Total volume in one tube of serum-saline-antigen mixture	1	1	1	1
E	Fractional volume of *serum mixture* in one tube of serum-saline-antigen	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}$
F	Volume of serum mixture in one tube of serum saline-antigen $= D \times E$	.5	.5	.5	.5
G	Mils of serum in one mil serum mixture $= \frac{B}{E}$	–	–	–	–
H	Mils of serum dilution needed for C tubes $= C \times F$	10	10	10	10
I	Mils of serum dilution needed for next dilution, plus a minimum amount for wetting of glassware $=$ next whole number over L^{a+1} or more if the worker desires. In the last column $I = O$.	9.	.9	6.0	0
J	Mils of serum dilution needed, total $= H + I$. In the last column $J =$ the next whole number over H, or more if the worker desires.	19	19	16	11
K	Mils of serum needed, total $= (G \times J) = \left\{\frac{B}{E} \cdot J\right\}$	0.38	–	–	–
L	Mils of previous serum mixture needed $= \left\{\frac{K}{G^{a-1}}\right\} = \left\{\frac{B^a \cdot J^a}{E^a}\right\} \div \left\{\frac{B^{a-1}}{E^{a-1}}\right\} = \left\{\frac{B^a}{B^{a-1}}\right\} \times (J^a) \times \left\{\frac{E^{a-1}}{E^a}\right\} = \left\{\frac{B^a}{B^{a-1}} \times J^a\right\}$*	See K	8.5	8.0	5.5
M	Mils saline $= J - L$. In the first column $M = J - K$	18.62	8.5	8.0	5.5

*When the values of E are a constant, as is customary in routine serum tests $\frac{E^{a-1}}{E^a}$ cancels out. If $\frac{B^a}{B^{a-1}}$ is made a constant such as 1/2, 1/3, 1/10, etc., a further simplification results. We must keep in mind that the ratio $\frac{B^a}{B^{a-1}}$ must be of such value that when multiplied by J^a the resulting quantity will be measurable in the available measuring devices.

MORE COMPLICATED DILUTIONS

The foregoing example is one of a very simple dilution in which it was desired to use an absolute minimum of serum while employing the standard volumes of antigen and serum-saline mixture. Concerning the more extended application of the chart, it is apparent that instead of *serum*, any liquid can be diluted; instead of *saline*, any diluent can be employed; and instead of *antigen*, an equal volume made up of any number of reagents can be substituted, one or all of which may have values which may vary within the limits of the experiment at the will of the operator.

A MODIFICATION OF THE WASSERMANN TEST*

By Clarence N. Callary, Philadelphia, Pa.

THE Wassermann test is now recognized as one of the most valuable laboratory aids that has yet been brought into routine use. The practitioners have long since come to recognize in this test a splendid method of syphilitic diagnosis and at the same time have come to regard its negative presence in many instances as a sore disappointment. It is not uniformly present in all cases of manifest syphilis from the clinical point of view. Is this a fault of the technic or is it due to a temporary or permanent disappearance in the reaction in certain persons and in certain phases of the infection, regardless of the application of specific medication? The answer as a result of experiences is that it is due partly to the first cause and partly to the second. I say this because I have been able to add to the column of positives by utilizing a modification of the classic Wassermann test which eliminates those errors inherent in the test itself. I maintain that Wassermann's original method is subject to an error arising from the presence in human serum of a varying amount of natural antisheep amboceptor capable of being reactivated by guinea pig complement. While the quantitative relations of the complement and antigen in the Wassermann reaction are important, they are vastly more so in the case of the hemolytic amboceptor. Noguchi[1] has pointed out very clearly the dangers of not delicately adjusting the quantity of amboceptor used in the reaction. Morgenroth and Sachs[2] have shown that the relationship between complement and amboceptor necessary for hemolytic reaction is one of inverse proportions. To state it more clearly, in their own words, "in the presence of larger quantities of amboceptor, smaller quantities of complement suffice" and vice versa. Noguchi, in his work, has found that, while, in the presence of one unit of amboceptor, 0.1 c.c. of guinea pig's complement is required to produce hemolysis, by using four, eight, and twenty units of amboceptor, complete hemolysis is obtainable with one-third, one-fifth, and one-tenth of the 0.1 c.c.

*From the Pathologic Laboratory, Garretson Hospital, Philadelphia, Pa.
[1]Proc. Soc. Exper. Biol. and Med., vi, 3, 1909.
[2]Morgenroth und Sachs in Ehrlich's Gesammelte, Arbeiten, etc., Berlin, 1904.

complement, respectively. For this reason an excess of amboceptor might result in complete hemolysis in a test, if a small fraction of the complement were left unfixed by the syphilitic antibody. Another result of an excess of amboceptor would consist in a partial dissociation of the complement from its combination with the antigen-antibody compound. As Noguchi puts it, "a quantity of syphilitic antibody just sufficient to fix 0.1 c.c. of the complement against two units of the amboceptor is no longer efficient in holding back the complement from partial liberation against the influence exerted by more than four units of the amboceptor." Human serum contains a certain quantity, and sometimes a large quantity, of amboceptor hemolytic for sheep red cells. From these considerations it follows that the serum from the patient must, in each case, be titrated in order to determine the hemolytic unit. For this purpose a number of mixtures are made in test tubes, containing each 0.1 c.c. of serum of patient (inactivated at 54 C. for 15 minutes), 0.2 c.c. of a 20 per cent complement (fresh guinea pig serum) and increasing quantities of a 5 per cent emulsion of sheep's red cells, thus:

Titration

TUBE	SERUM OF PATIENT	20% COMPLEMENT	0.85% NACL	5% S.R.C.	
1	0.1 c.c.	0.2 c.c.	0.5 c.c.	0.2 c.c.	Complete hemolysis
2	0.1 "	0.2 "	0.4 "	0.3 "	" "
3	0.1 "	0.2 "	0.3 "	0.4 "	" "
4	0.1 "	0.2 "	0.2 "	0.5 "	Partial "
5	0.1 "	0.2 "	0.1 "	0.6 "	No "

Test

TUBE	SERUM OF PATIENT	ANTIGEN	20% COMPLEMENT	0.85% NACL	5% S.R.C.	
6	0.1 c.c.	0.1 c.c.	0.2 c.c.	0.5 c.c.	0.2 c.c.	?
7	0.1 "	——	——	0.5 "	0.2 "	Serum control
8	——	——	0.2 c.c.	0.5 "	0.2 "	Comp. "
9	——	——	——	0.5 "	0.2 "	Salt "

Controls show no hemolysis.

These tubes are placed in water-bath at 40° C. for one hour and following this, there are added to the test the required quantities of a 5 per cent emulsion of sheep's red cells (2 units) and again place test in water-bath at 40° C. for one hour, then make final reading. In the given case Titration tube No. 3 (0.4 c.c. of a 5 per cent S.R.C.) represents one unit, and one half or 0.2 c.c. of a 5 per cent emulsion of sheep's red cells, two units, are the quantities to be used for the test tubes 6 to 9.

In ten per cent of human serums in which no amboceptor is present to complete test add one unit of amboceptor (that has been titrated with 0.2 c.c. of a 20 per cent complement against 0.5 c.c. of a 5 per cent emulsion of sheep's red cells) and 0.25 c.c. of a 5 per cent sheep's red cells, thus:

TUBE	SERUM OF PATIENT	ANTIGEN	20% COMPLEMENT	0.85% NACL	5% S.R.C.	I U. AMBO.
6	0.1 c.c.	0.1 c.c.	0.2 c.c.	0.5 c.c.	0.25 c.c.	"
7	0.1 "	——	——	0.5 "	0.25 "	"
8	——	——	0.2 c.c.	0.5 "	0.25 "	——
9	——	——	——	0.5 "	0.25 "	I U. of Ambo.

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EDITORIALS

The Influenza in Germany

IT SEEMS from reports that have reached the office of the Surgeon General that epidemic influenza became sufficiently important in Germany last July to lead to special conferences of prominent medical men at Berlin and at Munich. We have no detailed information concerning the extent of the prevalence or the degree of virulence which the epidemic manifested in Germany. At the present time it seems that the virulent form of the disease first appeared in Germany. It is true that a mild epidemic of influenza passed through Spain in the early Spring of 1918, then visited France and probably extended into Germany; but in both Spain and France the Spring epidemic was mild resembling that form of the disease which we have had in this country more or less for some years, and which acquired a rather wide diffusion in the year 1916. The German pathologists who attended the conferences at Berlin and Munich evidently had had plenty of material under observation and upon which they reported and consulted. It was concluded at these conferences that the pathology of the epidemic then

prevalent in Germany was the same as that of the epidemic of 1889-90. This conclusion was reached after the comparison of preserved specimens from the epidemic of 1889-90 with tissues taken fresh from the body. Obendorfer stated that he had made a large number of autopsies at Munich and reported the lesions of the respiratory organs as uniform and typical to such an extent that he would undertake to dictate a protocol.

In the initial stage of the disease the most characteristic findings are bean-sized hemorrhages projecting into the lung tissue. This is followed by a firmer infiltration of the parenchyma, the nodules projecting against and raising the pleura. There are many intermediate formations between the small nodules and the large hemorrhagic infiltrations. There are all possible gradations from simple blood extravasations into the lung tissue, still containing air, to firm infarcts—the last mentioned consist of hemorrhages and have a bluish black tinge. The larger infiltrations are wedge-shaped with the base of the wedge projecting against the pleura, thus indicating their relationship to the vascular system. The extravasation of red blood cells seems to be due to abnormal permeability of the walls of the blood vessels.

The second stage is characterized by an exudative pneumonic process combined with hemorrhages. The picture varies considerably. There may be a true croupous hepatization of lobular, or even lobar, extent, both red and grey, though the tinge is usually brownish and not distinct. The surface is not dry, but is covered by a slimy, dirty coating, resembling a picture of Friedlander's pneumonia. The pneumonic foci are sometimes flattened out at the ends into yellowish white wedge-shaped structures corresponding to anemic infarcts both in form and in color. These often become the seat of gangrene or suppuration, the pleura being coinvolved in the process. In the majority of cases there is a catarrhal and desquamative infiltration rather than a fibrinous exudation. However, in the majority of instances, especially in the severe ones, there is marked suppuration.

The bronchi are filled with pus even in the first stage, the smaller branches contain thin fluid, though at times firm exudates plug the lumen of the smaller bronchi. The effect of this is distended bronchi. In some instances there are many minute abscesses surrounded by hemorrhages. These abscesses often become confluent, ending up in the formation of large pus cavities.

The first lesions in the pleura consist of pinhead hemorrhages, and empyema may result. As a rule only one side is affected. Pericarditis is a natural consequence of the inflammation of the pleura. There are no gross changes in the heart with the exception of some thickening of the arteries.

The larynx and the upper third of the trachea usually show no involvement, but the lower third of the trachea is the seat of an intense mucopurulent exudation, which in many cases assumes a fibrinous character, with the consequent formation of extensive pseudomembranes in the lower trachea and down into the bronchi. Sometimes edema of the epiglottis is observed.

A rather characteristic feature is presented by the hyperplastic condition of the lymphatic apparatus of the tongue and the tracheal ring. The thymus

is well preserved, the cervical and axillary, but not the inguinal glands, are enlarged. On the whole, the impression of the existence of a status thymo-lymphaticus is conveyed. As young individuals are mainly affected these facts may stand in the relation of cause and effect. The spleen is enlarged and sometimes a septic spleen tumor may be found.

The liver is but seldom involved, and the kidneys show a general hyperemic condition. In the brain and the meninges there is a marked vasodilatation, but no meningitis is found. Pinpoint hemorrhages are sometimes seen near the base of the brain.

The histologic examination reveals the following unusual findings: In the trachea there is an intense exudation of fibrin in the deep layers of the mucosa, and a progressive inflammation of the deeper portions of the tracheal walls. In the lymphatic glands there is an enormous vasodilatation with hemorrhages, as well as proliferation of the endothelium, especially in the axillary glands.

The foci of inflammation in the lungs show a leucocytic infiltration round the alveoli, bronchi, and the walls of the small arteries. It does not involve the whole vessels, which are dotted with isolated spots of infiltration. There are also hemorrhages into the heart valves, with a consequent displacement of the fibers and damage to the endothelium with no definite endocarditis, but with lesions which facilitate the development of a secondary mycotic endocarditis. There are, therefore, signs of lesions of the walls of the vessels, which are found to be particularly marked in some cases in the pulmonary artery. An advanced mycotic arteritis was detected in these cases. Masses of streptococci were found.

Obendorfer concludes his report with the following statement:

"The essence of the whole pathologic picture consists, therefore, in the abundance of hemorrhages seen in the mucous and serous membranes, in the respiratory tract, and in the lungs, which indicate a damaged condition of the capillary vascular system. The abscesses, save for those originating in the bronchi, are also of a hematogenic nature. The whole process seems to be primarily a bacteriemia localized in particular in the pulmonary blood-vessels. Hemorrhages in the lungs pave the way for a secondary infection, the results of which dominate the whole field in the later stages. In any case the wedge-like shape of the pulmonary foci indicate a vascular origin of the lesions. From a purely anatomical point of view the condition bears many points of resemblance with pneumonic plague, though there is no indication as to an entry of the virus through definite lymphatic channels. The primary bacteriemic condition was not found to be due to B. influenza (Pfeiffer), and thus the invading virus remains undiscovered."

It is worthy of note that in Germany and in this country most of the deaths due to pneumonia following influenza have been among the most robust and most vigorous men. This is quite characteristic of all pestilences. The severe, rapid infectious diseases kill most quickly and most surely the strongest and most robust. This is the case not only in pandemic influenza, but in the

plague, typhoid fever, typhus fever, smallpox, and in short, all the acute, highly infectious diseases. This is explained by the resistance put up by the body cells against the invading microorganisms. A strong and vigorous man attacked by one of these diseases either makes a speedy and rather abrupt recovery, or is likely to die. Nature overdoes the resistance, kills the invading organisms too rapidly and sets free such an amount of poison that death results.

In many of the reports coming into the Surgeon General's Office it is noted that the mortality is high among the most vigorous men. Moreover, this epidemic differs materially from the ordinary influenza in the age incidences of those who die. In the ordinary influenza, children and the aged furnish the greatest number of deaths; while in the pestilential form of the disease most of the deaths are among those from twenty to forty years of age. It has been assumed by some that the infectious diseases, in the long run, benefit the race by killing off the weaklings. Even Herbert Spencer, the great philosopher of modern science, taught this doctrine; but the epidemiologist knows better. Infection, like war, kills the young, vigorous, robust adults.

—*V. C. V.*

Notes on Influenza

1. Pandemic influenza is an acute infectious disease, of unknown causation, characterized by a marked leucopenia which removes the normal barriers against infection and exposes the body to invasion by whatever pathogenic organisms may gain access to it.

2. It may cause death without the aid of other viruses, but in the majority of instances its deleterious effects are intensified by the presence and activity of other pathogenic organisms.

3. In its spread it is not dependent upon the presence or aid of other viruses. It attacks the strong and vigorous as readily as it does the infirm. The mortality caused by it is higher among the strong and vigorous than among the weak and sickly.

4. The mortality accompanying or following it is largely determined by the presence and virulence of other infectious organisms.

5. The period of incubation, so far as it can be determined, is two days or less depending, doubtlessly upon the virulence and the amount of the virus introduced into the body and the readiness with which the natural resistance of the body is broken down and the degree of defenselessness, indicated by the leucopenia, established.

6. The pathogenic organisms which most frequently take advantage of the defenseless state of the body induced by the influenza virus are those which are capable of growth and multiplication in the pulmonary tissue, such as the different types of pneumococcus, streptococcus, Friedlander's organisms, and possibly some varieties of staphylococcus and the Pfeiffer bacillus.

7. Punctures made from the lungs during life and during the active stage of the pneumonia may show any of the above-mentioned organisms, either in

pure culture or in mixed form. The question arises as to how far these organisms may be due to terminal infection.

8. The pathologic condition found in the lungs after death from pneumonia following influenza, is determined by the invading organisms.

9. Influenza is not transmitted through the air for long distances, nor is it due to weather, nor to meteorological conditions. It is transferred from man to man either directly or indirectly; either by direct contact or indirect contact.

10. In the epidemic of 1889-90, fifteen hundred deaths in New York City were attributed to influenza. This does not mean that the influenza virus alone and unaided caused this number of deaths, but is does mean that during the period of the epidemic the normal deaths were increased by this number. In Massachusetts, Abbott says in speaking of that epidemic, that 39 per cent of the population were affected. It was less prevalent in Southern than in Northern cities. It was not only less prevalent in the South, but less fatal. In Massachusetts the disease appeared earlier and was more fatal in the more intensely populated areas of that state. The ratio of deaths to the population of the state at large was about 12 per ten thousand; to those attacked it was 31 per ten thousand. The epidemic of 1889-90 was the most fatal scourge that had visited Massachusetts up to that time. It lasted about fifty days and increased the mortality in that state by about twenty-five hundred.

11. Speaking of the epidemic of 1889-90, Abbott, Secretary of the Massachusetts State Board of Health, (See Twenty-first Annual Report of the State Board of Health of Massachusetts) formulated the following conclusions:

"1. The first appearance of the influenza in Massachusetts as an epidemic, in the past season, may be stated to have been on the 19th or 20th of December, 1889, and the place of its first appearance was Boston and its immediate neighborhood.

"2. It increased rapidly in the number of persons attacked, and reached its crisis generally throughout the state in the week ending January 11, 1890, after which date it gradually declined in severity, and had nearly ceased as an epidemic by the 10th of February; so that the duration of the epidemic was about seven weeks. It reached its crisis earlier by several days in Boston than in the smaller cities and the remoter parts of the state. Its course was still later in Nantucket, Dukes and Barnstable counties.

"3. The ratio of the population attacked was about 40 per cent,—or more exactly, as indicated by the returns, 39 per cent,—or about 850,000 persons of all ages.

"4. People of all ages were attacked, but the ratio of adults was greatest; of old people next, and of children and infants least.

"5. The weight of testimony appears to favor the statement that persons of the male sex were attacked in greater number and with greater severity than females.

"6. The average duration of the attack (acute stage) was from three to five days.

"7. The predominant symptoms were mainly of three general groups,—

nervous, catarrhal and enteric, the last being much less common than the others; the special symptoms most observed in the nervous group being extreme depression, pain and weakness; in the catarrhal group, cough, dyspnea and coryza; and in the enteric group, nausea, vomiting and diarrhea.

"8. The chief diseases which followed in the train of influenza, and were intimately associated with it, were bronchitis and pneumonia. Phthisis, when already existing in the victim of the attack, was undoubtedly aggravated; and, in many cases, a fatal termination was hastened.

"9. The ratio of persons attacked in industrial and other establishments employing large numbers was about 35.5 per cent, or less than that of the population at large. That of the inmates of public institutions was still less, —29 per cent.

"10. The ratio of persons who were obliged to leave their work on account of illness from influenza was about 27 per cent of the whole number employed.

"11. The average length of their absence from work was five days.

"12. Special occupations do not appear to have had a marked effect in modifying the severity of the epidemic upon operatives in such occupations.

"13. Various theories have been advanced relative to the method of propagation or spread of influenza."

Dr. Abbott concluded, after considering the various theories concerning the spread of the disease, that it does not travel faster than the modern modes of locomotion can explain. The conclusion, therefore, is that human intercourse is the all important factor in the transmission of this disease.

12. Lord (*Journal Medical Research,* 14, 295) found Pfeiffer's bacillus in pure culture in 25 per cent, and mixed with other organisms in 59 per cent of 186 cases in an interepidemic period; while he found it in pure culture in 15 per cent and with other organisms in 35 per cent of 20 cases during an epidemic. This epidemic prevailed in Boston from the last week in November, 1907, to the middle of January, 1908. "It appears to be certain for New England at least, that a larger proportion of the population was attacked than in any previous outbreak of acute respiratory infection since 1889-92."

13. In 1916, influenza seems to have increased. In the vital statistics report for that year this disease is accredited with 18,886 deaths. However, it is uncertain how many of these deaths were due to some form of pneumonia. In the annual report of the Department of Health of the State of New York for 1916, there appears the following statement:

"Notwithstanding the epidemic of influenza and infectious colds that visited the city the early part of the year, and the epidemic of anterior poliomyelitis that visited the city during the summer, the death rate was the lowest on record."

14. Park (*New York Medical Journal,* October 12, 1918) has found the influenza bacillus in "almost every case of clear-cut infectious influenza. In the complicating pneumonia we have found them associated with either strepto-

coccus or pneumococcus. In one case bronchopneumonia was due entirely to the influenza bacillus."

15. Symmers (Ibid) calls attention to the fact that the disease kills the robust as well as the weak. He states that the disease begins in the lower lobes. "The sequence of events is that the infective organisms, acting first and particularly simultaneously upon the lower lobes of both lungs, cause a rapidly confluent variety of lobular exudative pneumonia attended by changes in the vascular structures marked by the escape into the alveoli of variable numbers of red cells and quantities of blood serum, either independently of one another or in combination." He states that no fibrin is found in the alveoli, that the lower lobes have a slate-blue color, that they are almost completely consolidated, the edges escaping consolidation, but undergoing corresponding emphysematous changes.

16. Berg and Bullowa (Ibid.) give the symptomatology, but do not mention cyanosis or epistaxis, which have been so frequently observed by others.

—*V. C. V.*

Ravages of the Influenza Epidemic

THE Bureau of the Census, Department of Commerce at Washington reports that influenza deaths in America greatly outnumbered the war's casualties among American troops.

"The influenza epidemic has thus far taken a much heavier toll of American life than has the Great War. The total loss of life throughout the country is not known, but the Bureau of the Census has been publishing, for 46 large cities having a combined population estimated at 23,000,000, weekly reports showing the mortality from influenza and pneumonia. These reports, which cover the period from September 8 to November 9, inclusive, show a total of 82,306 deaths from these causes. It is estimated that during a similar period of time the normal number of deaths due to influenza and pneumonia in the same cities would be about 4,000, leaving approximately 78,000 as the number properly chargeable to the epidemic.

"The total casualties in the American Expeditionary Forces have recently been unofficially estimated at 100,000. On the basis of the number thus far reported, it may be assumed that the deaths from all causes, including disease and accidents, are probably less than 45 per cent and may not be more than 40 per cent of the total casualties. On this assumption, the loss of life in the American Expeditionary Forces to date is about 40,000 or 45,000.

"Thus, in 46 American cities having a combined population of only a little more than one-fifth the total for the country, the mortality resulting from the influenza epidemic during the nine-weeks' period ended November 9 was nearly double that in the American Expeditionary Forces from the time the first contingent landed in France until the cessation of hostilities.

"For the 46 cities taken as a group, the epidemic reached its height during

the two weeks ended October 26, for which period 40,782 deaths were reported —19,938 for the week ended October 19 and 20,844 for the following week. Since October 26, however, the decline has been pronounced. During the week ended November 2, 14,857 deaths occurred, and during the following week only 7,798. The only city in which the number of deaths reported for the week ended November 9 exceeded the number occurring during the previous week was Spokane, Washington.

"In general, the epidemic traversed the country from east to west. In a number of eastern cities—notably Boston, where the greatest mortality occurred during the week ended October 5—the largest numbers of deaths were reported for earlier periods than that which covered the height of the epidemic for the 46 cities taken as a group. On the other hand, in New Haven, New York, Pittsburgh, and Rochester the maximum mortality occurred somewhat later than in eastern cities generally. In Baltimore, Buffalo, and Philadelphia the two-weeks' period ended October 26 showed the greatest number of deaths. For the entire nine-weeks' period, the greatest mortality due to the epidemic, in proportion to population—7.4 per one thousand—occurred in Philadelphia; and the next greatest—6.7 per one thousand—was reported for Baltimore."

The Pneumonias

WHILE our knowledge of acute inflammation of the lungs, known as pneumonia, is still meager and wholly lacking in many particulars, we are justified in at least tentatively and timidly making some suggestions. During the Spanish-American war we recognized typhoid fever and included all of a certain group of diseases under this designation. We now distinguish between typhoid and the paratyphoids, and of the latter we know that there are at least two. We distinguish between the bacilli causing the typhoidal diseases and we know that a vaccine which protects against typhoid does not protect against paratyphoid, and vice versa. The facts seem to justify us now in using the word pneumonia in the plural, and in speaking of the pneumonias. Of the pneumococcus there are at least four types, and possibly many more. Then there seems no doubt that the streptococcus does cause both lobar and bronchopneumonia. How many types of this organism are capable of causing pneumonia we do not know. There are cases of pneumonia in which Friedlander's bacillus is found in pure culture, and some pathologists are quite sure that this organism induces characteristic lesions which distinguish pneumonia due to this bacillus from the pneumonias due to other bacteria. During the prevailing influenza pneumonia skilled observers have obtained pure cultures of Pfeiffer's bacillus from the lungs by puncture during life. In the present state of our knowledge we may say that pneumonia may result from the growth in the lungs of the following bacteria:

(1) The pneumococcus of which there are at least four known types.

(2) The streptococcus of which there are many types, the hemolyticus apparently being the most virulent,

(3) The Friedlander organism.

(4) The Pfeiffer bacillus.

There is some evidence that a staphylococcus may cause pneumonia. Then, we must add the more specific pneumonia caused by the plague bacillus and which is believed to cause 100 per cent mortality.

We are beginning to realize that any bacterium which is capable of growth and multiplication in living lung tissue may be the cause of pneumonia. When such an organism multiplies in pulmonary tissue and sensitizes the body cells, the body cells begin to destroy the involving bacterial cells and the result of this change is the liberation of the protein poison with local inflammation and systemic poisoning. The poison set free is the same whatever the name or character of the invading bacterium may be.

If this conclusion be true, to what extent and from what cause may we reasonably expect the lesions to vary with variations in the kind of bacterial growth in the lung? This is an important question, and the following tentative explanation is offered. Each bacterium has its predilective tissue upon which it feeds. No living thing can grow and multiply without access to food, and nothing is food to a given organism unless it furnishes elements which can be prepared, absorbed and assimilated by the cells of that organism. As a result of this fundamental and basic biological fact we may expect that the widely different complex tissues of the lung will vary in their suitability as food supply to the widely different invading cells. When we recall that Pasteur showed that certain bacteria act upon one form of tartaric acid and are wholly without action upon another, the two differing only in the relative arrangement of their atoms, we gain some adequate comprehension of the essential relationship between food and consumer, between nutritive medium (whether it be natural and a constituent of the living body or artificial and in the test tube)—and the organism which it supports. Whether the pneumococcus, the streptococcus, the Pfeiffer bacillus and other organisms, each selects some histologic element in the lung tissue upon which it feeds, in which it multiplies and in which it is broken up by the sensitized body cells, we do not know. The solution of this question should be one of the problems constantly held in mind by those who are now studying the pathology of pneumonia. Since in most cases the infection is a mixed one, this problem will not be easy of solution. At present it is certainly difficult to name the infecting agent from a study of the lung tissue after death. Still there are some suggestive findings. It is well known that the Pfeiffer bacillus will not grow on artificial culture media unless hemoglobin be present and the fact that hemorrhages into the lung tissue and in other parts of the body are more common in influenza pneumonia than in other pneumonias may have some meaning. The fact that typical lobar pneumonia is most commonly associated with some type of the pneumococcus and

that the streptococcus is often present in bronchopneumonia may have a significance not hitherto attached to them.

The purpose of this writing is to make the claim that so far as the bacteriologic factor is concerned there are many species of bacteria which may cause pneumonia, and in this sense there are many pneumonias.

—*V. C. V.*

Why We Should Join the Red Cross

HOW American Red Cross physicians engaged in relief work in Jerusalem are accomplishing worth-while results in the face of great difficulties—and what they are up against, is shown in a report just received here from W. S. Dodd, A.R.C., physician working at Mejdel.

With two capable English trained nurses, and three native helpers, more or less useful, Dr. Dodd, his "hospital" housed under tents, performed 252 operations in seven weeks, besides giving medical examinations, treatment and counsel to hundreds of the destitute inhabitants and refugees.

His report says in part: "The work of the hospital was of the plainest sort, it might be called primitive. About twenty-five tents comprised the hospital proper, with a dispensary tent, and tents for the living quarters of the staff.

"The soil was all the purest sea-sand with thistles and scant grass; going barefoot was the universal custom, and in our own quarters we of the staff used to follow that custom with great pleasure. * * * *

"The professional side of the work was of the greatest interest to me and every day was a pleasure. The clinics numbered sixty to a hundred a day. Of course, we had all classes of cases in medicine and general surgery, but by far the larger proportion of our patients were eye-cases.

"Of the 252 operations that I did in less than seven weeks, 222 were for the eyes. This is the number of persons operated on, most of them having more than one operation, perhaps on all four lids, so that I really operated on 408 eyes.

"There were some cataracts, not more than would be seen in the same number of cases elsewhere, but trachoma and its consequences accounts for almost all of the eye troubles in this land. I set out to treat these cases radically and secured fine results when I could keep the patients long enough for a reasonable after-treatment. But even so, the number of eyes that can be saved from partial and total blindness is large and the economic value of each eye thus saved is enough to make the prosecution of this line of work of the greatest importance for the redemption of the land.

"The accident cases are always interesting. I had the last end of treatment of some cases of bombed hands, of which there had been quite a number in the earlier days. These were largely in children, and were due to their picking up unexploded Turkish bombs that were lying in the fields from the time of the British advance in the Gaza region. Many fingers and even hands were lost from this cause.

"Vermin was the great enemy we had to fight. Fleas were hardly counted as a problem because we could do nothing against them, they were everywhere and inevitable, and so far as we know at present not being the carriers of any special disease, did not come within the hostility of a medical conscience.

"Lice and maggots were a daily terror. How many wounds and injuries came to us filled with maggots I can not tell. A favorite dressing for a wound is a piece of raw meat, a breeding place for maggots, and they can hardly be blamed for invading the adjoining premises.

"Many a child had to be put under chloroform in order to search out and pull from their hiding places deep in the middle ear a half dozen wriggling maggots whose every motion was causing torture to the innocent victim.

"A woman came to the clinic complaining of headache. A single sore on her face led to questioning, and when she rather unwillingly undid her turban we found an exaggerated case of impetigo, and every separate sore was as if the whole thickness of the scalp down to the bone had been punched out, and every sore was a nest of maggots. I removed 60 at the first seance, and at the first dressing next day the nurse had more to do. The headache was cured without further treatment. And these are not the most loathsome cases that we saw.

"Another great difficulty with which we had to contend was the filthy habits of the people. In spite of providing proper sanitary facilities, we were compelled to have a scavenger go around every morning and clean up the filth from around the tents of the patients. The women were as bad offenders as the men. We made it a rule that anyone known to have violated these simple sanitary regulations must go without their dinner next day, and this was quite an effective punishment."

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ORIGINAL ARTICLES

WAR DEAFNESS AND ITS PREVENTION—REPORT OF THE LABYRINTHS OF THE ANIMALS USED IN TESTING OF PREVENTIVE MEASURES.* (MIDDLE EARS PREVIOUSLY REPORTED)†

By Stacy R. Guild, Ann Arbor, Mich.

METHODS

A FULL description of the procedure by which each animal was handled at the time of exposure to the detonations was given in the report of the middle ear conditions; reference may be made to it for that part of the technic. In that report the protective measures tested were also listed and described. As stated there the animals were killed about 48 hours after exposure to the detonations. The treatment of the tissues at the time of killing the animals was directed primarily to the securing of the best possible cochlear fixation. The method used was the one with which I had had the best results in a series of experiments on cochlear histologic technic, conducted as a preliminary to objective work on the physiology of hearing which the war has postponed indefinitely, but which I hope at some future time to carry out. The fixation fluid used was Zenker-formol in the proportions suggested by Maximow (1909), as a modification of Helly's fluid, for other work. A stock solution is made in the following proportions:

Mercuric bichloride,	50 gm.
Potassium dichromate,	25 gm.
Sodium sulphate,	10 gm.
Distilled water,	1000 c.c.

*Submitted to the National Research Council.

From the Department of Anatomy, University of Michigan Medical School, Ann Arbor, Michigan.

†Three previous reports have been made; the first was published in this Journal, September, 1917; the second, January, 1918; and the third, March, 1918. The second report is the one containing the account of the middle ears the labyrinths of which are here reported.

This was filtered carefully to exclude any particles which might block small vessels. Just before using there was added to this stock solution 10 per cent by volume of 10 per cent formalin; the glacial acetic acid of the regular Zenker's fluid was not added. Both solutions were kept in an oven at 39° C. until the time of mixing for use. The fixative was injected through the vascular system, following a thorough washing out with a 0.75 per cent solution of sodium chloride, also kept at 39° C. until placed in the flask for injection. This preliminary washing out is essential for the securing of good penetration of the fixative.

The routine procedure was to place the animal under chloroform anesthesia; then to open the thorax and pericardial sac and insert the cannula of the injecting apparatus in the systemic aorta through the wall of the left ventricle, the ligature being placed by passing the thread through the transverse sinus of the pericardium, thus including the pulmonary aorta. This can be done very rapidly after a few trials and I was able regularly to have the saline solution running soon enough to avoid any clotting of blood in the cochlear vessels. The vessels to the caudal half of the body were routinely clamped off by a hemostat placed so as to include both aorta and inferior vena cava just above the diaphragm. This reduced the amount of fluid necessary for satisfactory injection of the cochlear region. The injection was made with air pressure averaging 145 mm. of mercury. About 150 c.c. of warm saline solution were used in washing out the blood and this was followed immediately by 200 c.c. of the warm fixative described above. Only a small portion of this reaches the cochleae, of course, since all the blood vessels of the upper half of the body are injected. The cochleae and some of the surrounding bone, including most of the vestibular parts, were then removed and the two pieces placed in 50 c.c. of warm fixing fluid and left at room temperature. These remained in the fixing fluid from a week to ten days, the fluid being changed two or three times, because a precipitate forms slowly after mixing the formalin with the Zenker stock solution. They were then washed for 24 hours in running tap water and placed in 10 per cent alcohol; and were transferred from this to 80 per cent alcohol by 10 per cent changes at 24 hour intervals. They were then placed in 80 per cent alcohol to which had been added a sufficient amount of a saturated solution of iodine in absolute alcohol to make the mixture a cherry red color. In this they remained until they ceased to decolorize the solution, more iodine being added as needed. This time averaged about ten days. They were then passed at 24 hour intervals through 90 per cent and 95 per cent alcohol into absolute alcohol which was changed three times. Instead of passing them directly into the mixture of equal parts of absolute alcohol and ether, they were passed through four intermediate mixtures, each increasing the ether ratio 10 per cent until the 50 per cent was reached. This was an extra precaution to avoid as far as possible shrinkages due to a more sudden change. Ordinary celloidin embedding followed, slow evaporation being used, taking a month or more to reach a firm consistency. The blocks were then hardened in 80 per cent alcohol and transferred through 50 per cent and 30 per cent alcohols into 4 per cent nitric acid for decalcification. They remained in this 12 days, except two

groups, one of which remained 6 days and the other 9 days. The fluid was changed daily. They were then transferred to a 5 per cent solution of sodium sulphate, remaining in this 48 hours with one change of fluid; and were then washed in running tap water for 24 hours. The blocks were then "double embedded" in paraffin. They were passed from the tap water through 30, 50, 80, and 95 per cent alcohols, and the dehydration completed with carbol-xylol (crystal carbolic acid one part, xylol three parts). Absolute alcohol can not be used because of the celloidin present. An intermediate step of equal parts of 95 per cent alcohol and carbol-xylol was used to make the change more gradual. After dehydration with carbol-xylol they were changed to xylol and while thus cleared the blocks were trimmed in such a way that the position of the modiolar axis could be determined later for orientation of the sectioning. They were infiltrated and embedded in 52° C. paraffin in the usual way, the celloidin block containing the cochlea being handled as a piece of tissue.

This method gave in most cases a very fair preservation of the delicate epithelial structures in the cochlea; in a few instances it has failed, these are probably cases where the vascular injection did not penetrate well. The preservation of the tectorial membrane is poor by this method, it is usually found curled back in part of the turns, and it is not so thick as some methods show it to be.

From blocks prepared by this method it is possible to cut thinner serial sections than have usually been employed in studies on the cochlea. From such a block I have an unbroken series of 5 micra sections of a whole guinea pig cochlea, and I have cut some at 3 micra, but not a series. The material used in this study is cut in 7 micra sections; because of the shortage of glassware, especially of large cover-glasses, only every fifth section was saved. It would have been impossible to mount all the series otherwise. From the wide extent of the injured areas reported in the experiments of Wittmaack, Yoshii, and others, it was thought that every fifth section would be sufficient to fully indicate the extent of the injuries. For an exact study of the distribution of injury that I have found unbroken series are needed; every fifth section gives the general distribution of injured areas, but the study of unbroken series might yield additional facts of interest. The sectioning was done with a sliding microtome, using the "water-on-the-knife" method. The blocks were oriented so as to parallel the modiolus as nearly as possible in sectioning; in most cases this was closely approximated, in a few there was some deviation. In most blocks the sectioning was continued until the stapes was reached; in some it was forced to stop sooner either because of imperfect decalcification of the block or because of hard particles in the niche of the round window or elsewhere in this region; these particles are probably grains of sand from the tap water, which was unusually laden with dirt at the time part of the washing was done. The sections were fixed to slides by the usual water-albumen paraffin section method, and were stained with Heidenhain's iron lac hematoxylin; counterstained with benzopurpurin, and mounted in damar. The technic differed from the usual treatment of paraffin sections on slides only in the use of carbol-xylol, instead of absolute alcohol, in passing from xylol to 95 per cent alcohol and back again.

This was necessary because of the celloidin present. To completely remove mercuric crystals the sections were passed through an iodine solution in 80 per cent alcohol before the transference to iron alum. The benzopurpurin was used in solution in 95 per cent alcohol; the sections permitted to overstain, and the excess stain removed by fresh 95 per cent alcohol; the slides being transferred to carbol-xylol to stop the decolorization at the desired stage.

RESULTS

The condition of the labyrinthine parts, here reported, should be compared with the middle ear conditions, previously reported; this can readily be done for the individual ears, as the animal designation has been made in all tabulations.

The injuries to the inner ear have been, for the most part at least, limited to the cochlea. In no case were all of the special sensory areas in the vestibular part of the labyrinth sectioned, owing to the close trimming of the blocks necessary to save glassware. Of those sectioned, many of the maculæ acusticæ and some of the cristæ acusticæ have some shrunken hair cells, but I have no reason to believe that these are more than artefacts. The stapes was reached in the sectioning in 76 of the 92 cochleæ cut; of the 76, all but 10 are in the normal position. In each of these ten cases the annular ligament is broken and the base plate of the stapes tilted more or less into the vestibule. While this condition may be due to the detonations, I am inclined to believe that it was caused by accidents in handling at some time before the celloidin embedding, most probably during the removal from the animal. Therefore these displacements will not be considered further. In both ears of one animal no joint cavity is present about the base plate of the stapes, but this is not a condition which can be attributed to the detonation. The position of the membrana tympani secundaria, closing the fenestra rotunda, is normal, or nearly so, in all cases; it is slightly wavy in some, but no more so than the changing fluids might account for. In part of the membranes there is some edema evident, especially of the middle ear surface. Free blood cells and clots are present on the middle ear surface, but these are the result of the damage to the middle ear parts, already considered. None of the labyrinths have what may be called "gross" lesions, such as the rupture of the walls of the ductus cochlearis or the scala vestibuli or the scala tympani. The occasional bending of parts of the basilar membrane occurs as often in controls as in exposed animals, and is probably due to the embedding. Definite lesions of the organ of Corti and of the spiral ganglion are present in many of the cochleæ. No evidence of extensive internal hemorrhage was found in any of the labyrinths; in some a few isolated blood cells were observed adhering to the scala tympani surface of the basilar membrane. (See Figs. 10 and 13.)

To present the appearance of the lesions observed drawings will be used; they are selected to show the more usual types of injuries.

In speaking of the turns of the cochlea the method of designating by half-turns, beginning at the basal end, has been selected as best adapted to the purposes of this report. Fig. 1 shows in outline a modiolar section with the turns numbered according to the method used. The part in the midmodiolar section

is considered as the middle of each half-turn; the junctions of the half-turns have the organ of Corti cut tangentially. Such junctions may be seen in Fig. 2. In speaking of sections of the organ of Corti the term "radial" refers to those in the region of the modiolar sections; the term "tangential" refers to sections in the region of the junction of two half-turns; the term "oblique" refers to sections in the intermediate region. Fig. 3 is of a normal organ of Corti in radial section, Fig. 4 is of a normal organ in oblique section, and Fig. 12 is of a normal organ in tangential section. The oblique and tangential sections are favorable for the observing of certain of the lesions because several of each element of the organ of Corti are included in each section. The first part of the first half-turn which deviates from the axis of the cochlear spiral and is almost parallel to the modiolus for a distance in the vestibule, has been listed separately in the records made; it is termed the "vestibular part"; Fig. 2 shows the relation of this part of the ductus cochlearis to the rest of the labyrinth. The fenestra rotunda is "beneath" the last portion of the vestibular part.

Figs. 3 to 14, inclusive, are at the same magnification—295 diameters; they are therefore directly comparable, and are at a magnification sufficient to permit ready recognition of parts. The normal sections are inserted for comparison with the injured ones.

The loss of single or of a few adjacent outer hair cells is the definite injury of most frequent occurrence and is evidently the least severe of the definite lesions. Figs. 6, 7, 8, and 13 show sections having such lesions in radial, oblique, and tangential sections. Special features in the various sections are mentioned in the legends (q.v.). Such loss of hair cells is usually associated with a displacement of the corresponding Deiters' cells, frequently showing as a nuclear displacement, as in Fig. 7. Derangements of Deiters' cells without loss of hair cells have not been called injuries in the records made for the reason that they may possibly be artefacts. For some time I was not certain that the absence of isolated hair cells indicated an injury, but after finding such gaps in many of the best preserved cochleæ I have arrived at the conclusion that these are not artefacts. This belief is further strengthened by the increasing frequency of such absences as an area of more severe injury is approached in following the organ of Corti in serial sections. As may be seen in the illustrations given it is possible to have several degrees of severity of such injuries, depending on the proportion of outer hair cells which are missing. It ranges from the loss of a single cell in one section with all the other sections of the region normal, up to the loss of the majority of the cells in all sections for a considerable distance. All these various lesions I have grouped under the term of first degree injury, which may be defined as the loss of part of the outer hair cells with or without derangement of the Deiters' cells.

The absence of all the outer hair cells is the condition found next in order of frequency to the preceding. Fig. 8 illustrates this lesion. This condition may be present in all the sections of a half-turn or more; it ranges from this large extent to a single section. Since only every fifth section has been saved, the presence of this condition in a single section of a series means that it may have

extended over any or all of the four sections to either side which were not saved. It will be noted in the illustration that the organ of Corti retains its general outline; this is one of the differentiating points between this injury and the more severe types. This condition, absence of all outer hair cells with retention of the general shape of the organ of Corti, has been termed second degree injury, for purposes of reference.

Of less frequent occurrence than the preceding condition is that illustrated in Fig. 9. Not only are the outer hair cells missing but also the organ of Corti is crushed out of shape; the illustration shows the usual condition of the filling of the tunnel, Nuel's space, and the outer tunnel space with cellular debris. In some cases there is more or less vacuolization of the mass. It will be observed that the inner hair cell is present, as it is in the other lesions so far described. This condition does not, in my material, occur in isolated sections, but areas so injured are always adjacent at one end, and usually at both, to areas of lesser or of greater injury. This condition, absence of outer hair cells associated with a general crushing of the organ of Corti with massed or vacuolized debris in the large spaces of the organ, has been termed third degree injury.

A more severe lesion of the organ of Corti is that illustrated in Figs. 10 and 14. In this lesion the outer hair cells are all absent, the organ of Corti is badly broken up, the cellular debris is usually vacuolized but may be massed as in the typical third degree injury, and the inner hair cell is absent. The cells of the internal spiral sulcus are frequently vacuolized. This condition has been termed fourth degree injury, and is characterized by the severe disintegration of the organ of Corti with absence of the inner hair cell, which is, of the special sensory epithelial cells, the least often missing. In only one instance was the inner hair cell observed in an abnormal condition when the rest of the organ of Corti in that section was normal. Two adjacent sections of a series (every fifth section saved) show a chromatolysis of the inner hair cell. In one of these two sections there is no other injury evident; the other section has part of the outer hair cells missing. Elsewhere definite lesions of the inner hair cells have been observed only in association with severe injuries to the rest of the organ of Corti. This fourth degree injury, like the third degree, is not found in isolated sections in otherwise normal areas, but areas of it are bounded by areas of lesser degree of injury.

Fig. 11 shows the most complete destruction of the organ of Corti which is present in my material; it occurred in a zone of fourth degree injury, and since it occurred but once I have not given it a special designation of degree.

The distribution of the lesions of the organ of Corti in the various cochleæ studied is shown in the charts of Plate IV. In making these charts the relative lengths of the various half-turns have been approximated, instead of showing each half-turn as of the same value. To indicate the various degrees of injury three shades of grey, parallel lines, and dots have been used. The darkest shade of grey represents the condition that has been termed fourth degree injury; the intermediate grey, third degree injury; and the light grey, second degree injury. The narrowest of these light grey zones represent single sections, though they are proportionately too wide for the actual ratio which

a single section should cover in the chart. The parallel lines indicate areas where all sections are in the condition termed first degree injury; and the dots indicate first degree injury in isolated sections. Where two or three adjacent sections are in this condition it has been shown by drawing a line underneath the dots, unless it is between zones of more severe injury, in which case parallel lines have been used. The number of dots is not, in most cases, the exact number of sections with lesions but the number of dots indicates the relative frequency of sections showing injury to the organ of Corti. Since only every fifth section has been saved, the absolute distribution can not be determined from these series. The position of the ends of the injured areas can be determined only by means of graphic reconstruction which allows for the difference in length of the part of the organ of Corti contained in radial, oblique, and tangential sections. I have devised a suitable method for making such graphic reconstructions, but have not used it here since most of its value over the method of approximation would be lost due to having only every fifth section. In studying the cochleæ the organ of Corti and other structures were followed section by section from the vestibular end of the cochlear duct to the apical end, being traced back and forth through each series for the different turns. The notes, from which the charts presented were made, were jotted down at the time of observing injured areas during these examinations of series.

For convenience of reference, the conditions recorded have been grouped in four charts.

In Chart I are placed all cases where the outer ear was entirely open and the detonation used was one shot from a 45 caliber Colt automatic pistol with the muzzle at 15 cm. from the ear. Most of these are the open ears of animals in which the other ear was "protected;" in all cases the 15 cm. was measured from the opposite ear, and the barrel pointed downwards about 20 degrees along the left side from above and in front.

In Chart II are presented the controls with the open rubber ear and glass tubes of various sizes. From a study of the great variations in individual cases in the cochleæ recorded in Chart I, where all were exposed to as similar traumatic conditions as possible, it is evident that the number of controls with each tube is too small, there being only one with each, except with the 2 mm. tube, and in this case the extra two animals were used because wax entered the end of the tube during the experiment (cf. middle ear observations).

In Chart III are presented the conditions of the cochleæ of the "protected" ears. To facilitate comparison, these have been arranged in the same order as the middle ear observations on the protected ears (q.v.).

In Chart IV are presented the conditions of the cochleæ of animals submitted to detonations other than the usual one shot at 15 cm.

Besides these, two animals were taken as controls of the possible injury to the ears while in the basket during the experiment with others. One of these, animal 62, was also placed in the holding apparatus as a control of possible injuries by this procedure. The other, animal 63, simply remained in

the basket during six experiments, being exposed thus to the sound of six shots from the pistol at a distance of about 25 feet, the gun pointing away from the basket. Both cochleæ of animal 62 are entirely normal. The left cochlea of animal 63 has a few sections with missing or distorted outer hair cells in the sixth half-turn; the right cochlea has about 30 isolated sections with some outer hair cells missing, scattered throughout its length except in the vestibular part and the eighth half-turn; the injured sections are most numerous in the third to the sixth half-turns.

Shrinkage and chromatolysis of part of the cells in parts of the spiral ganglion are present in many of the cochleæ; this condition is present most often in the vestibular part and first half-turn; less frequently it is present in the second, third and fourth half-turns, and occurs very seldom above this level. In general the distribution corresponds with the injuries to the organ of Corti, but there are many exceptions to this general arrangement. In the vestibular part and first half-turn shrunken ganglion cells are much more frequently present in the cochleæ of unprotected ears than the protected ones in which definite lesions of the organ of Corti occurred; and in these unprotected ears the number of shrunken ganglion cells frequently appears to be a much greater proportion of all the cells than the proportion of hair cells missing in the corresponding region. On the other hand, in many cases the ganglion cells show no injury in regions corresponding to parts of the organ of Corti that were severely injured. The possibility must always be kept in mind that these ganglion cell alterations may be artefacts; but after observing many cases where the occurrence of a zone of injury corresponds to a zone of ganglion cell shrinkage and protoplasmic change I am of the opinion that these indicate a true lesion. Animals allowed to live a longer period of time after being submitted to detonations are needed to definitely settle this point. In two cases all the ganglion cells were in bad condition, but in both of these the general fixation was so poor that the alteration is in all probability an artefact. In a few cases some of the nerve fibers leading from the ganglion to the organ of Corti are definitely degenerating; in most cases they appear nearly, if not entirely, normal. The fibers in the organ of Corti itself can not be seen in the sections of the more severe lesions.

A peculiar condition is present in the cochleæ of animal 44. The ductus cochlearis, sacculus, and utriculus are distended to an unusual size. Reissner's membrane is bulged into the scala vestibuli and is longer than normal. It is not thickened. The walls of the utriculus and sacculus are similarly distended. The distention is somewhat less in the right cochlea. The right cochlea of animal 37 has a similar, but much less distended, condition from the basal end to the fifth half-turn, and the second and third half-turns of animal 27 show it in slight degree. In the one with the greatest distention, the left cochlea of animal 44, the stria vascularis of most of the third half-turn and of part of the first half-turn has a peculiar enlargement of the blood vessels. The enlargement of the blood vessels of the stria vascularis and the distention of the endolymphatic channels of the left cochlea of animal 44 may

be associated as cause and effect but it seems doubtful in view of the facts that enlarged vessels are not present in the other cases of distention and that several cases of enlarged vessels, though of much less extent, are present in cochleæ where no distention has occurred. I wish to specifically state that I am undecided whether either the enlargement of the vessels of the stria vascularis or the distention of the endolymphatic channels has been caused by the detonations.

DISCUSSION OF RESULTS

In discussing the above observations upon the labyrinths their bearing upon the relative efficiency of the various protective measures will be considered first and the evidence from the three sets of observations which I have made correlated. Then a comparison will be made of the lesions in my material with those recorded by other observers upon detonation injuries of the labyrinth, and the bearing of the results upon the general problem of the physiology of hearing indicated.

I. *Relative Efficiency of Protective Measures.*—The condition of the middle ear parts and the tambour results, reported previously, both indicated a division of the protective measures into two distinct groups on the basis of their relative efficiency in preventing the passage of the force of the detonation waves used; these two sets of results agree in the devices which would be placed in each group. Dry cotton, the Elliott protector, and the Wilson-Michelson instruments are in the less efficient group. Examination of Chart III shows that the division into groups on the basis of the cochlear results is not so well marked; each of the protective measures failed to prevent definite cochlear lesions in one or more of the ears with which it was used. Even here, however, a ranking of the devices is evident; and two of the three protective measures which are in the less efficient group on the basis of the other tests again rank lowest.

It may be that one of the groups of observations is of more value than the others; if so, this should receive the most consideration in drawing conclusions. I would call attention to the fact that the animal experiments are the ones which indicate the devices that permit an injurious amount of detonation waves to pass; the physical experiments are of value in helping to place the preventives in their relative order of efficiency. The tambour method, on the other hand, has the advantage which all experiments in physics have over biologic work; *i. e.*, the materials used are not subject to the individual variations which the reactions of living organisms are. It is evident from the great variations in the cochlear injury in the cases where the ear was open and the conditions were as similar as possible that there is either a great individual difference in guinea pigs in the degree of susceptibility to injury of this type or an entirely unrecognized factor acting to modify the detonations (see Chart I). In the conduction of the animal experiments with protective measures there are opportunities for errors in technic; they were recognized and guarded against, but the possibility must be kept in mind that in some cases the wax packing used may not have completely prevented the entry of injurious force through the

crevices around the tube which it was supposed to close, or that the device may not have been properly placed in the rubber ear. The former error is the more probable; the latter is one that is more likely to occur in the use of devices by troops than under laboratory conditions. If it were not for the great individual differences in the long series of controls (Chart 1), I would be inclined to think that the possible errors mentioned above had occurred often, and that therefore the cochlear results were almost worthless as a basis for comparison of the relative efficiency of the devices. But, if such were the case, the question immediately arises as to why the middle ears were not also damaged in a like ratio. As a possible explanation of the discrepancy here might be advanced the general belief for many years among otologists that in cases of air wave trauma of the ear the injury to the labyrinth is less when the tympanic membrane ruptures than when it remains intact; the explanation advanced is that the force is expended in rupturing the tympanic membrane. The statements are based upon clinical experience. Yoshii (1909) reported one animal which has a bearing upon the subject. In this case a guinea pig was exposed to the detonation from the firing of a revolver at 20 cm. (size of gun and position with reference to the animal not given). At autopsy it was found that the right middle ear was badly damaged while the left middle ear was entirely normal. Study of the cochleæ showed the right one to be entirely normal, while the left one showed "very light degree alteration." From his description the alteration is less than anything I have called a definite lesion. This case agrees with the clinical view. In my material, animals 17 and 18 were the only ones in which, under similar conditions for the two ears, one tympanic membrane remained intact and the other ruptured. In animal 17 the cochlea of the side with the normal middle ear was severely injured, while the other cochlea was only slightly injured. In animal 18 difficulties in technic prevent any definite statement as to the cochleæ. Since the tympanic membrane was ruptured in all cases of open ears exposed to the usual detonation, no comparison is possible in this series. However, there are many cases here, and in the controls with the open rubber ear and glass tube, in which the cochlea was severely injured. Of the ears with which dry cotton, the Elliott protector, and the Wilson-Michelson instrument were used, all had damaged middle ear parts; one of each group of three had the tympanic membrane ruptured, though less severely than in most of the cases of open ears. With dry cotton, the cochlea of the ear with a radial slit in the tympanic membrane is definitely injured; the injury to this cochlea is greater than to one of the other two, and less than the injury to the third one. With the Elliott protector the cochlear injury is much less in the case with a ruptured tympanic membrane than in the two where it remained intact. With the Wilson-Michelson device the cochlear injury in the case of the ruptured tympanic membrane is about the same as in one of the other two and less than the injury in the third case. With the rest of my material such comparisons can not be properly made, because the force of the detonation waves reaching the ears varied greatly, due either to different protectors or to dif-

ferent distances used. While some of my cases are in accordance with the idea that rupturing of the tympanic tends to protect the labyrinth, it seems to me, on the whole, that the exceptions to the rule are too numerous to accept it as an explanation of the inconsistency between the middle ear and the cochlear conditions. In this my material agrees with the clinical experience of Meyer with troops submitted to modern battlefield conditions. It seems improbable that a true "bone conduction" can have played much, if any, part here, since the vibrations would have had to pass through a person's body to reach the ground on which the animal rested.

The condition of the cochleæ of animal 63, used as a control for possible injury while in the stock basket during the testing with other animals (see page 159), was a surprise to me, as I fully expected this control to be normal; animal 62 had both cochleæ entirely normal. There is a possibility that the lesions present, outer hair cells missing in isolated sections, are not due to detonations, in which case all the lesions of this nature would have to be ruled out of consideration. On the other hand, if they are due to the detonations of the pistol at the distance at which the basket was placed, (25 feet with the gun pointing in the opposite direction), all the cases of such "isolated section" lesions must be considered as possibly due to such an origin and their bearing on the protection afforded by devices thrown out. At the time of the experimentation I considered the distance sufficient to avoid any such complication; at present I must leave the question of interpretation open. Here, as in the other groups, variation has occurred; one animal normal and one injured (?).

As the most suitable way of determining the ranking given by the combined tests to the protective measures, the method of adding the rankings given by the different tests has been chosen. All three sets of observations are given the same value by this method. The devices tested only by the tambour method are omitted in this tabulation. To determine the order of efficiency as given by the tambour method the results with the three guns used are ranked. When two devices are tied for a place, the sum of this and the next lower ranking is halved and each of the devices given this number. (See Tables I and II.)

The ranking arrived at by this method is open to criticism, and is, at best, only an approximation. The division into two groups is very definite, however; and the other requirements for military use should be the deciding factor in choosing from the more efficient group, rather than the slight differences in the laboratory results with these protective measures. These other factors have already been considered in the previous reports and need not be taken up here. It suffices to state that the "Tommy" is the best of the mechanical devices from the standpoint of general military requirements for field use by troops, and since it has a slight advantage over the others in the laboratory tests it is the protective measure which seems to be indicated for a large field trial. On the other hand, the results of the laboratory tests seem to eliminate the need of field trials by troops of dry cotton, the Elliott protector, and the Wilson-Michelson device.

II. *Comparison with Previous Work on Detonation Injuries.*—The extent and distribution of the injuries to the organ of Corti in the animals I have used are quite different from those reported by Wittmaack, Yoshii, and Prenant and Castex, but are similar to some of Hoessli's and of Hoshino's cases. With the exception of some of Hoessli's experiments all the animals used by other workers have been exposed to detonations with the ears entirely open. Wittmaack's statements are very indefinite regarding his detonation cases; some animals were negative, and no statement is made of the extent of the injured area in the ones which were injured. The one figure which he presented of a detonation injury is from the next to the highest turn (fifth and sixth half-

Table I

Ranking of the Devices by the Tambour Method

PROTECTIVE MEASURE	RANKING ACCORDING TO			SUM OF RANKINGS	RESULTING RANKING
	22 CALIBER	38 CALIBER	44 CALIBER		
Vaselined cotton	1½	1	2	4½	1
"Tommy"	3	2½	1	6½	2
Glycerined cotton	1½	4	3	8½	3
Mallock-Armstrong	4	2½	5	11½	4
Wax cone	5	5	4	14	5
Wilson-Michelson	8	6	6	20	6½
Elliott Protector	6	7	7	20	6½
Dry cotton	7	8	8	23	8

Table II

Ranking of Devices by the Average of the Three Sets of Results

PROTECTIVE MEASURE	RANKING ACCORDING TO			SUM OF RANKINGS	RESULTING RANKING
	TAMBOUR METHOD	MIDDLE EAR CONDITIONS	LABYRINTH CONDITIONS		
"Tommy"	2	1	4	7	1
Mallock-Armstrong	4	2	3	9	2½
Glycerined cotton	3	5	1	9	2½
Wax cone	5	3	2	10	4
Vaselined cotton	1	4	6	11	5
Elliott Protector	6½	7	7	20½	6½
Wilson-Michelson	6½	6	8	20½	6½
Dry cotton	8	8	5	21	8

turns of my terminology); it resembles somewhat the lesion I have termed third degree injury. A study of this and other figures given by Wittmaack leads me to agree with the group of workers in Siebenmann's laboratory at Basel; *i. e.*, there are many artefacts due to faulty histologic technic in the work of Wittmaack, so that even his indefinite statements must be discounted. As in all of his work on cochlear injury by sound waves Wittmaack considered the injury to the ganglion cells the primary lesion and the epithelial degeneration secondary. The lesions found by Yoshii in the middle ears were very similar to those of my unprotected animals. The two figures given by him of the organ of Corti after exposure to single detonations show a condition which agrees with that which I have termed fourth degree injury. (An ex-

tensive quotation from Yoshii's description of the lesions observed by him was given in the report on the literature, page 851 of the September, 1917, Journal of Laboratory and Clinical Medicine, to which the reader is referred.) He reported this severe lesion as present the whole length of the cochlea, which is a lesion more extensive than is present in any of the animals I have used. He also reported changes in the ganglion cells, and he, like the rest of the Siebenmann group of workers, considered these to be secondary degenerations and the epithelial primary. He also mentioned hemorrhage into the spaces of the labyrinth in some cases. The size of the gun used by Yoshii was not definitely stated; he merely said, "Diese Versuche wurden teils mit einer Kinderpistole und blossen Zündhütchen, teils mit Revolver und Patronen unmittelbar vor der Ohrmuschel und zwar jeweilen an beiden Ohren rasch nacheinander ausgeführt." He placed the muzzle of the gun much closer to the ear than I did, and in reality exposed each ear to two detonations; for my experiments show that both ears are damaged at much greater distances than that between the two ears of the guinea pig. This closer range may account for the more extensive injury his animals received. He used eight animals in this series; two were killed immediately, and one each after 2, 3, 8, 25, 45, and 60 days respectively. In view of my results it seems probable that more animals might have given him more variation. In any case, his statements as to some regeneration having occurred in the animals killed after the longer intervals certainly needs confirmation with a greater number of animals for each stage.

Hoessli, in his first series with detonations, was testing primarily air and bone conduction, to determine which transmits the injurious force. He used three guinea pigs with the incus removed on the left side of each, and two animals with moistened cotton in both ears. All were placed in a cage and a Swiss army revolver was fired five times at about 30 cm. above them. They were killed 24 hours later. Each animal was reported by a separate protocol. In none of the cases was there any damage to the middle ear parts, other than the operative injury in the animals with the incus removed. All three of the cochleæ in the cases with the incus removed were normal, as were also three of the four ears which had moistened cotton in the external meatus. In two of the three open ears with normal middle ear parts and one of the cotton protected ears the cochleæ had lesions in the organ of Corti in the lower half of the second turn (third half-turn of my terminology). The injury as described agrees with what I have termed third degree injury; Hoessli noted that the inner hair cells were present, and stated that there was no evidence of injury to the ganglion cells or nerve fibers, except the fibers in the organ of Corti itself. Except for this half-turn he reported the cochleæ normal. Of the third case of open ear with normal conducting apparatus, he said: "Die Scala cochleæ ist im ganzen normal und zeigt keine Veränderungen. Einzig an derjenigen Stelle, wo wir in Fall 22 die ausgedehnten Veränderung vorfinden, sehen wir hier einen teilweisen Mangel der äusseren Haarzellen bei sonst normalen Cort. Organ. Die übrigen Skalateile

sind ebenfalls normal." Apparently this was a slight injury; Hoessli was properly very cautious as to the interpretation of possible artefacts. In those of Hoessli's cases which are comparable to mine, cochlear injuries occurred in the same region where mine show the most frequent injury; *i. e.*, the third half-turn. The condition of the unprotected middle ear parts in his cases shows that he was working with a less powerful wave than I have used, for no injury to the middle ear parts occurred. Hoessli believed that the one case where the wet cotton failed to protect was due to the scratching loose of the cotton by the animal. He followed this series by one in which he used four cats, the left ears stopped with wet cotton, the right ears left open. To prevent scratching out of the cotton the animals were lightly narcotized and five shots were fired at 25 cm. above the four of them. As before, the animals were killed 24 hours later. The left ears in all cases were normal. In three of the four right ears there was an area in the upper part of the basal turn (upper part of second half-turn) extending through about 15 sections (thickness of sections not stated) where a slight variation from normal was found; the variation consisting of a depression of the organ of Corti in the region of the outer hair cells. The fourth case was entirely normal. In view of the variations in individual cases in the longer series I have used the two exceptions in Hoessli's short series are interesting.

While Hoessli was interested primarily in the question whether air or bone conduction transmits the injurious waves, he called attention to the bearing of the results with wet cotton to the protection of soldiers. All that he says of this phase of it is here quoted verbatim: "Hier denkt man unwillkürlich an die vielen Fälle von Schusstrauma bei Soldaten, welche Watte in den Ohren getragen haben sollen. Wir sehen eben hier, dass wenn der Wattepfropf nicht ganz fest sitzt, und am Ende gar nicht angefeuchtet ist, der Schutz des Ohres ganz illusorisch ist."

The region in which the majority of the lesions have occurred in my material is in general the same as was injured by the various guns used by Hoshino (1917).* He exposed guinea pigs to the detonations of a medium-sized revolver, a hunting gun, an army rifle, and a cannon. With the small arms blank cartridges were used and in most cases the shooting was directly toward the ear, at distances varying from "close up" to 100 cm.; two series were run with each gun, in the first group of series one shot was fired toward each ear of each animal, in the second group several shots each, the number varied from 5 to 350. The cannon was one used as a "time piece" and was loaded with only about four pounds of powder; the animals were placed two meters in front of the muzzle; they were blown as much as twenty meters by the explosion. Two animals were exposed to one shot each and two to five shots each. The animals of the various series were killed at intervals varying from "immediately" to fifty days after exposure. The greater number of animals were handled by an injection fixation, using Held's formal-bichromate-acetic

*It is to be regretted that the observations of this Japanese otologist are recorded in a language which renders them inaccessible to so many investigators. I desire to here express my thanks to Dr. I. Watanabe, an assistant in this laboratory, for reading this article to me.

mixture. The resulting injuries to the labyrinth were more severe and widespread in the cases where many shots were fired than in those "once exposed" (really twice since each ear was considered separately in counting the shots), but were in the same region of the cochlear canal for each gun, whether one or many detonations were used. Hoshino reported that the region of most severe injury varied for the different guns; it was lowest for the cannon and highest for the revolver. The regions for each were: (1) revolver, second turn and lower part of third; (2) cannon, upper part of basal and lower part of second turn; (3) army rifle, upper part of basal turn; and (4) hunting gun, lower part of second turn. One monkey was used, it was exposed to one detonation from the rifle held close to the ear. The injured area extended the whole length of the cochlea in this case, but Hoshino thought the wide extent possibly due to the short distance rather than to the different type of animal. The injuries to the organ of Corti varied from minor atrophic changes to complete destruction and replacement by a simple epithelium. Hoshino also broke the tympanic membranes of six animals and introduced staphylococci into the middle ears, waited until a suppurative otitis had developed, and then exposed them to detonations from the small arms. He found in general the same type and extent of injury due to detonation as in the animals with normal middle ears similarly treated. He added this suppurative otitis evidence in support of the view that impaired conducting apparatus does not protect the labyrinth from detonation injuries. Hoshino reported lesions involving the tectorial membrane, which was sometimes "frayed out" and sometimes almost entirely missing. While the technic used on my material is not favorable for the study of the tectorial membrane, because of the way it is shrunken and frequently turned up even in normal cases, I have observed no evidence that it has definite lesions due to detonations. While Hoshino stated that the area injured was more extensive with repeated detonations than with one, he did not mention variations in extent under identical conditions, such as my material shows. The small amount of powder used in the cannon and the fact that no shell was used would indicate that the intensity of the detonation was not so great as that of the majority of artillery pieces and exploding shells, but the placing of the animals in front of the muzzle where they were hurled twenty meters by the explosion simulated to a degree the conditions in the battle field where men are frequently hurled by the blast of an exploding shell and at the same time exposed to the intense sound. It is of interest to note that the lesions produced by Hoshino's cannon were of the same nature as those produced by the smaller detonations of both himself and others; this indicates that the study of lesions due to relatively small detonations are of value in interpreting the effects of more intense explosions.

Prenant and Castex (1916) placed animals in cages near large caliber guns at Fontainebleau. In no case was the tympanic membrane ruptured or the middle ear inflamed; ten guinea pigs and six rabbits were used. The preservation of the labyrinths was poor; they reported extensive cochlear lesions of the type to be expected from previous work in this line with smaller

guns. Since this is the only work in which animal cochleæ have been reported after exposure to detonations of such large guns as they used, it is very much to be regretted that the histologic technic used gave such poor results, for this makes them of very little value except for very indefinite comparisons and conclusions.

The report of J. S. and John Fraser (1917), made upon autopsy material from soldiers deafened by detonations, must be considered in the light of the histologic technic employed by them, which was such as to render the results very indefinite, as they realized. Hemorrhage into the labyrinth and about the entrance of the nerve roots in the fundus of the internal meatus were definite findings of interest. It is almost impossible in their material to differentiate the artefacts from the actual lesions in the organ of Corti and nervous tissues. Wilson reported recently (*Journal of the American Medical Association*, August 24, 1918) the condition of a temporal bone secured at autopsy six hours after the death of a soldier who had been deafened by a shell explosion. (Wilson said that two were reported in the Harvey lecture which he gave; but this is not yet available to me.) Formalin fixation was used. He, like Fraser, reported hemorrhage in the base of the internal auditory meatus. There was very evident damage to the cochlear parts; edema and small cell infiltration were mentioned as being present in the ganglion, stria vascularis, basilar membrane and organ of Corti. The epithelial cells and the ganglion cells were "indistinct," doubtless due in part, at least, to the time after death before placed in fixative and to the necessarily slow penetration of the fixative, even though the superior semicircular canal was opened.

The presence in my material, except in the most severe injuries, and also in Hoessli's detonation cases, of the inner hair cells is interesting in connection with Hoessli's observations on injury by the sound from organ pipes; he found the inner hair cells intact after the outer hair cells had disappeared and even sometimes when the supporting apparatus of the outer hair cells had broken down. These facts indicate either that the inner hair cells are more resistant to injurious sound waves, or that they do not receive as great intensity of the waves as do the outer hair cells. This is not taken into account in any of the theories of hearing. The statement of Shambaugh (1911) that the ciliæ of the outer hair cells are in constant contact with the tectorial membrane while those of the inner hair cells are free is suggestive in this connection.

None of the reports of previous experimental work involving detonation injury of the cochlea make any mention of separated zonal lesions, which are so plentiful in my material. (See, for example, "34 Rt." in Chart I.) It is evident that if the variations in sound waves are perceived by any type of peripheral analysis, the occurrence of definite zones of injury to the organ of Corti indicates that the parts injured were most active in converting the sound waves into nervous energy. In other words, if either the Helmholtz theory in its original form or in any of its modifications, or the Lehmann or the Ewald or the Köhler theory, or the theories involving the tectorial membrane as a differentiating mechanism, are correct, injured zones of the organ of Corti

are to be interpreted as being in the areas of resonance for the sound waves that caused the damage. If there is any definite pitch, or if there is a mixture of vibration frequencies in the sound waves produced by the firing of a 45 caliber pistol, it seems reasonable to suppose that it will not vary with different shots to the extent that would cause the difference in cochlear lesions observed under otherwise identical conditions; that is, open ears at the same distance and direction from the gun. No attempt has been made to obtain and analyze sound curves from the detonations used, so that no conclusions can be reached along this line.

A general view of Chart I, in which are presented the cochlear conditions in the open ears exposed to the firing of one shot at 15 cm. from the muzzle of a 45 caliber Colt automatic pistol, reveals that the average center of the injured areas, other than isolated sections of first degree injury, is in the third half-turn, except for the few cases with severe injury in the vestibular part and first half-turn. The making of the charts with the relative lengths of the half-turns indicated permits the ready recognition of the fact that the center of the total length of the cochlear duct of the guinea pig is also in the third half-turn. In Chart III, in which are presented the cochlear conditions in the "protected" ears, the average center of the injured areas is somewhat higher; and there is almost complete absence of injuries, even of the first degree in isolated sections, in the whole of the basal turn (vestibular part and first and second half-turns) of all the cochleæ, except those in the Elliott and Wilson-Michelson series.

These observations of separated zones of injury and the average grouping of the same are presented and attention called to them in the hope that they may prove of value at some time, in connection with other data, in solution of the problem of the physiology of hearing.

It is a pleasure to express here my appreciation of the valuable suggestions made by my chief, Dr. Huber, during the course of this work.

RESUMÉ OF ALL MY REPORTS UPON WAR DEAFNESS AND ITS PREVENTION

1. Laboratory methods for the testing of measures for the prevention of detonation injuries to the ear have been devised and such tests have been carried out upon various protective measures.

2. These tests indicate that the measures tested may be divided into two definite groups upon the basis of their efficiency in preventing the passage of the force of the detonation waves used; the variations within each group are less decisive. In the more efficient group are the Scientific Ear Drum Protector "Tommy," the Mallock-Armstrong Ear Defender, cotton soaked with glycerine, cotton soaked with vaseline, and the wax cone of the Italian navy type. In the less efficient group are dry cotton, the Elliott Perfect Ear Protector, and the Wilson-Michelson device.

3. The cochlear lesions produced by the detonations differ in extent and distribution from those hitherto reported; the injury areas are frequently separated by normal zones; these lesions are recorded in a graphic form which

makes them more available for reference than if the usual method of written protocols had been followed. The facts are presented without drawing theoretical conclusions as to their bearing on the physiology of hearing.

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Explanation of Figures

ABBREVIATIONS

a., Apical end of ductus cochlearis.
c.C., Cells of Claudius.
c.D.c., Cuticular processes of Deiters' cells (basal part).
c.H., Cells of Hensen.
c.i.s., Cells of internal spiral sulcus.
f.r., Membrana tympani secundaria closing the fenestra rotunda.
g.sp., Ganglion spirale.
i.h.c., Inner hair cells.
i.p., Inner pillars.
l.o., Lamina spiralis ossea.
l.sp., Spiral ligament.
m.b., Basilar membrane.
m.ret., Membrana reticularis.
m.v., Membrana vestibularis (of Reissner).
n., Nerve fibers in the spiral osseous lamina.
n.c. Cochlear nerve.
n.D.c., Nuclei of Deiters' cells.
n.o.p., Nuclei of the outer pillar cells.
N.s., Nuel's space.
o.h.c., Outer hair cells.
*o.h.c.*1, Outer hair cells of the first row.
*o.h.c.*2, Outer hair cells of the second row.
*o.h.c.*3, Outer hair cells of the third row.
o.p., Outer pillars.
o.t.s., Outer tunnel space.
ph.pr., Phalangeal processes of Deiters' cells.
sac., Sacculus.
s.t., Scala tympani.
s.v., Scala vestibuli.
t.f., Tunnel nerve fibers.
t.s., Tunnel space of the organ of Corti.
utr., Utriculus.
v.p., "Vestibular part" of the ductus cochlearis.
v.sp., Vas spirale.

Legends for Plate I

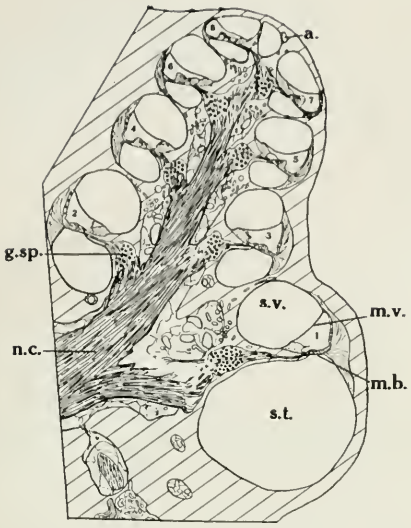
Fig. 1.—Outline drawing of a mid-modiolar section of a left cochlea of a guinea pig. Guinea pig 55, left cochlea, slide 1, row 4, section 1, 15×. The arabic numerals in the various sections of the ductus cochlearis indicate the designation of half-turns as used in this article. The part in the modiolar section is considered as the center of each half-turn; the junctions of the half-turns are in the sections which cut the curve of the organ of Corti tangentially.

Fig. 2.—Outline drawing of a section of a right cochlea of a guinea pig to one side of the modiolar axis, showing the position of what has been termed the "vestibular part" of the ductus cochlearis and the relations of parts in "oblique" and "tangential" sections. Arabic numerals as in Fig. 1. Guinea pig 21, right cochlea, slide 2, row 1, section 2, 15×.

Figs. 3 to 14, inclusive, were drawn with the aid of a camera lucida at a magnification of 885 diameters, and have been reduced in reproduction to 295 diameters, one-third of the original size of the drawing. Being at the same magnification, comparison is facilitated. Figs. 3, 4, and 12 are drawings of sections of the organ of Corti in normal condition, and are presented for comparison with the ones having lesions. All the cochleæ were prepared by the same technic and the sections used for illustrations were selected to present the typical lesions observed. See the text matter for the technic and the terminology used in designating the lesions.

Fig. 3.—Drawing of a normal organ of Corti in radial section. Guinea pig 21, right cochlea, slide 1, row 4, section 8, second half-turn, 295×. As is well known, the shape of the organ of Corti varies in the different parts of the ductus cochlearis; allowance must be made for this in comparing this drawing with those of lesions in other parts of the cochlea.

Fig. 4.—Drawing of a normal organ of Corti in oblique section. Guinea pig 41, right cochlea, slide 1, row 5, section 2, second half-turn, 295×.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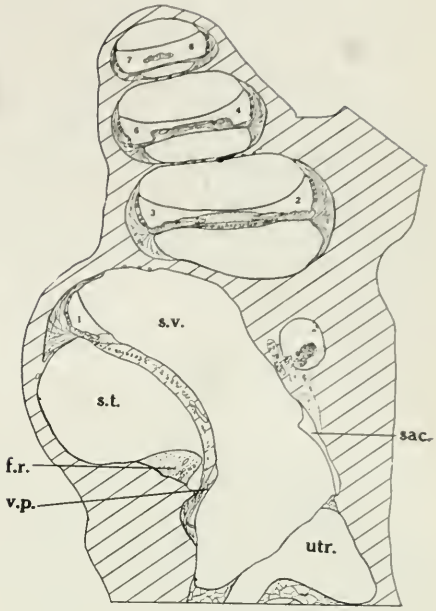
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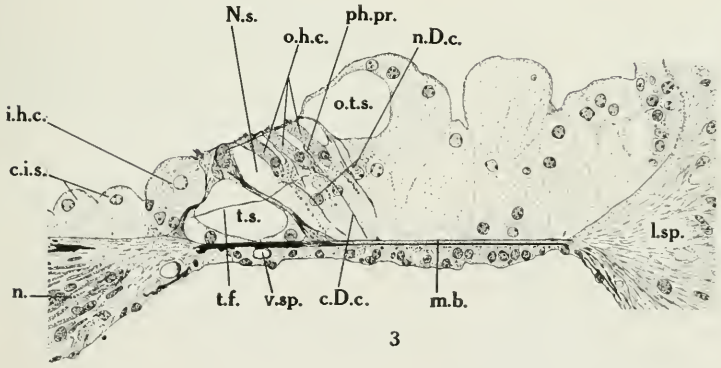
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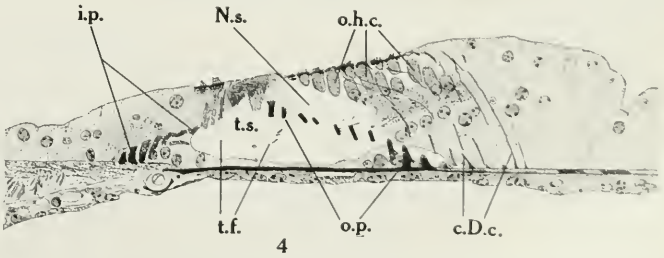
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Plate I.

Legends for Plate II

Fig. 5.—Organ of Corti, with first degree injury, radial section. Guinea pig 52, left cochlea, 1-4-7, third half-turn, 295×. The outer hair cells of the second and third rows are missing.

Fig. 6.—Organ of Corti, with first degree injury, radial section. Guinea pig 30, left cochlea, 1-6-2, first half-turn, 295×. The outer hair cell of the first row is absent, and the nucleus of the corresponding Deiters' cell is displaced downwards.

Fig. 7.—Organ of Corti, with first degree injury, oblique section. Guinea pig 47, right cochlea, 1-5-5, second half-turn, 295×. Compare with Fig. 4. Some of the cells of each row of outer hair cells are missing.

Fig. 8.—Organ of Corti, with second degree injury, radial section. Guinea pig 40, left cochlea, 1-3-2, fourth half-turn, 295×. All the outer hair cells are missing and the Deiters' cells are partially destroyed. Note that the general shape of the organ is retained; it is different from that of Fig. 3, but is the normal outline for this part of the cochlea.

Fig. 9.—Organ of Corti, with third degree injury, radial section. Guinea pig 29, left cochlea, 1-3-6, fourth half-turn, 295×. The shape of the organ is lost, being crushed; there is cellular debris in the spaces of the organ; the outer hair cells are missing; the reticular membrane in this case is broken and pieces of it are seen scattered through the mass.

Fig. 10.—Organ of Corti, with fourth degree injury, radial section. Guinea pig 28, left cochlea, 1-4-2, third half-turn, 295×. The severity of this type of lesion may be seen at a glance; all the essential parts of the organ of Corti have been destroyed. Adhering to the scala tympani surface of the basilar membrane may be seen two red blood cells and one leucocyte; this is one of the few cases where even this much hemorrhage was observed.

Fig. 11.—Drawing of a section in which the organ of Corti has been almost entirely replaced in 48 hours by a simple epithelium. Guinea pig 50, left cochlea, 1-4-9, third half-turn, 295×. This is the only instance in my material in which the destruction is so complete. I have not given it a designation of degree as was done with the types of lesions which occurred often.

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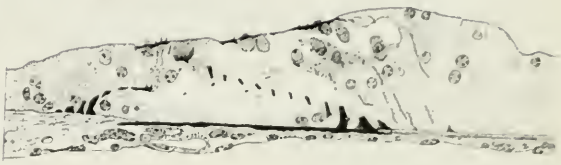

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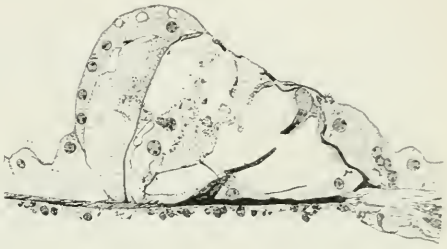

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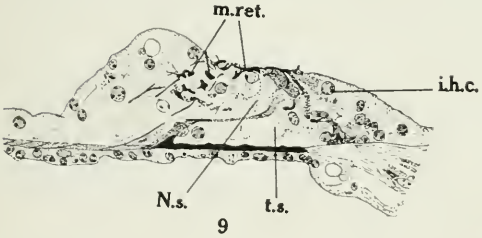

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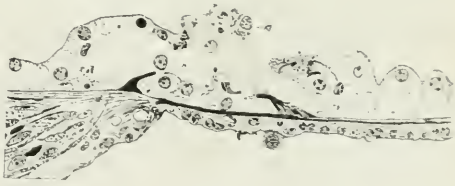

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Plate II.

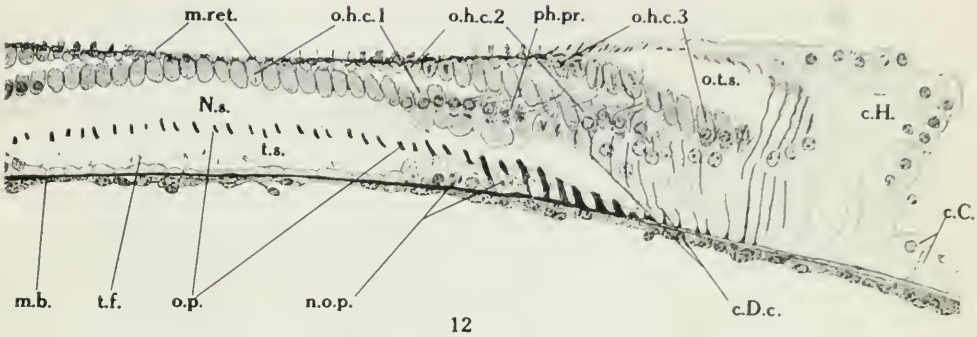
Legends for Plate III

Figs. 12, 13, and 14 should be compared directly in order to interpret readily the lesions shown in 13 and 14. All three are drawings of sections which have been selected as being of corresponding parts of the various organs of Corti. The elements of the organ of Corti have been labelled in Fig. 12 only; reference should be made to it in studying Figs. 13 and 14. Oblique and tangential sections are favorable for observing lesions because of the number of each element present in a single section.

Fig. 12.—Normal organ of Corti in tangential section; the plane of section is parallel to the modiolar exis. Guinea pig 33, left cochlea, 1-5-6, junction of fourth and fifth half-turns, 295×.

Fig. 13.—Organ of Corti with first degree injury, tangential section. Guinea pig 27, left cochlea, 1-5-2, junction of fourth and fifth half-turns, 295×. When compared with Figs. 5 and 6, which are of radial sections of the organ of Corti, the nature of this lesion is better understood; a few or even single outer hair cells are missing in a place. Such lesions are not artefacts due to the dropping out of bits of the tissue during or after the sectioning, since the pieces are embedded in celloidin and there is no evidence of such vacancies in the celloidin, which is itself faintly stained and would therefore show gaps.

Fig. 14.—Organ of Corti, with fourth degree injury, tangential section. Guinea pig 28, left cochlea. 1-2-7, junction of third and fourth half-turns 295×. Compare with Fig. 10, which is of this type of lesion in radial section. Comparison with Fig. 12 emphasizes how much destruction has occurred.



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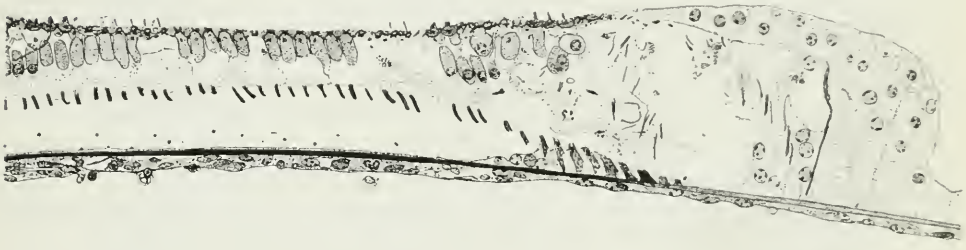

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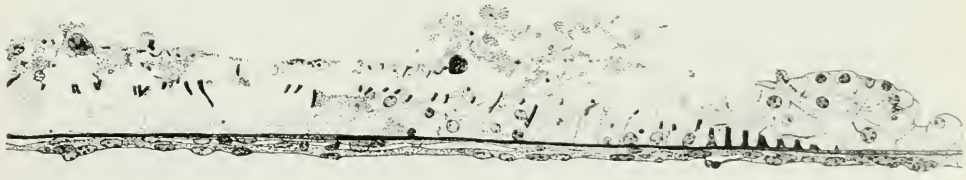

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Plate III.

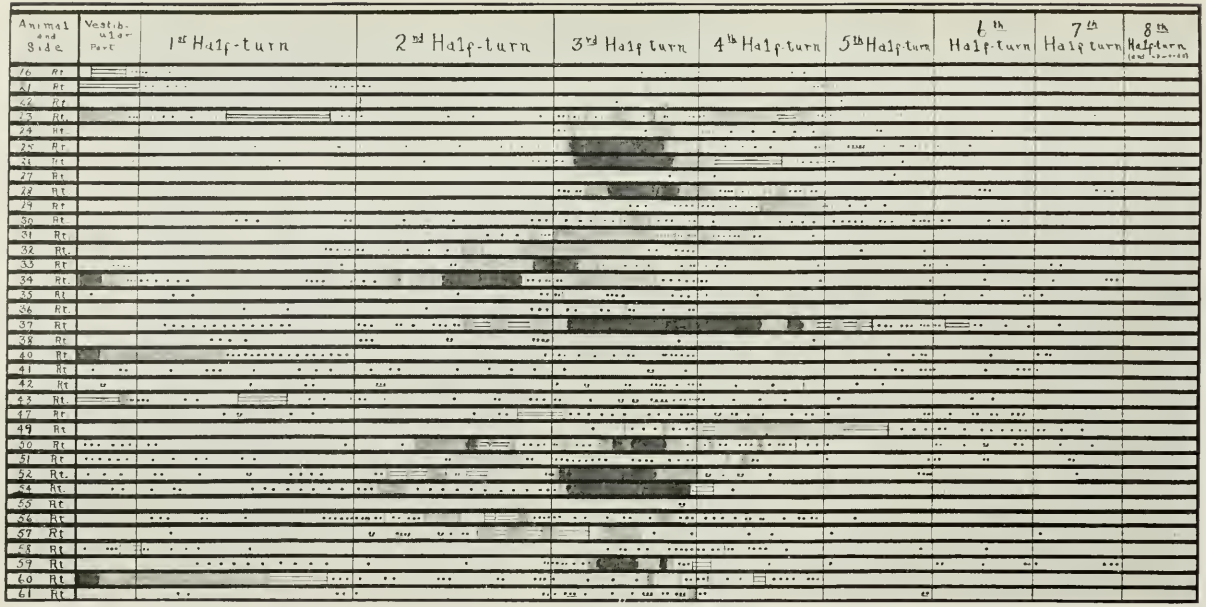

Chart I—Plate IV.

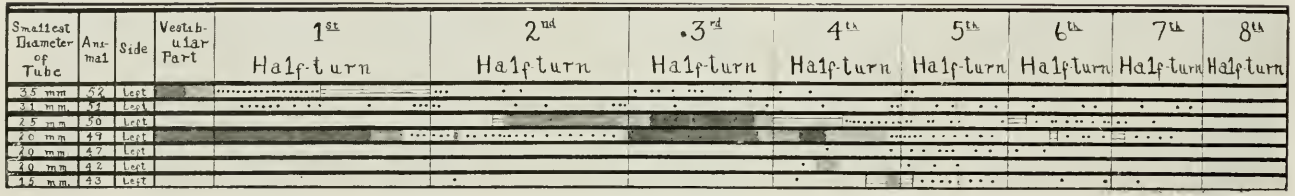

Chart II—Plate IV.

(For description of charts see page 180.)

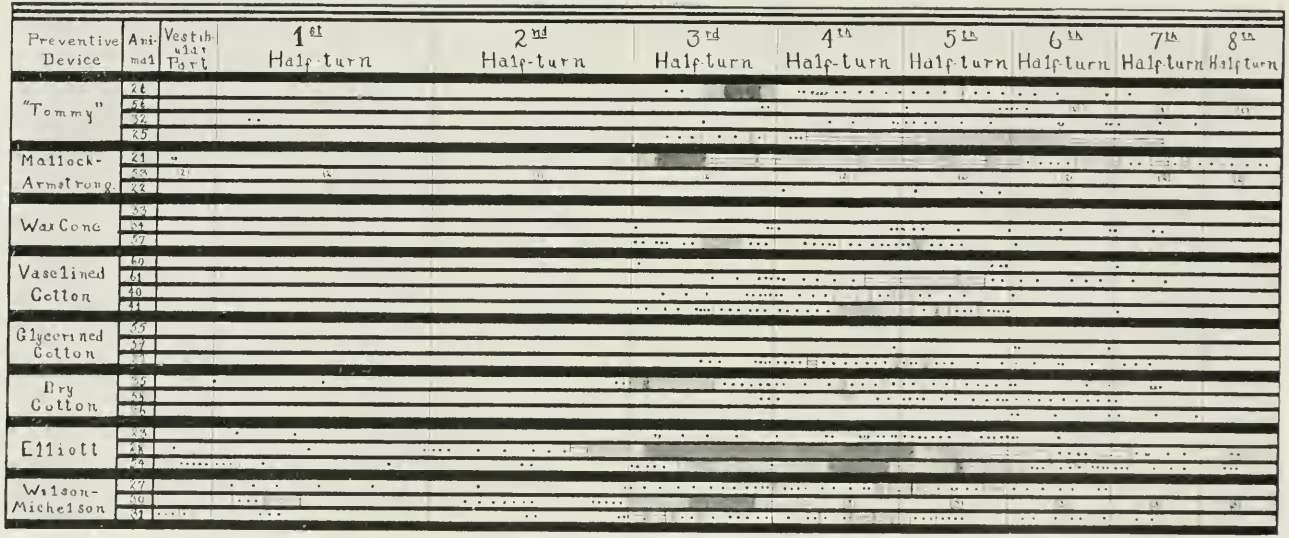

Chart III—Plate IV.

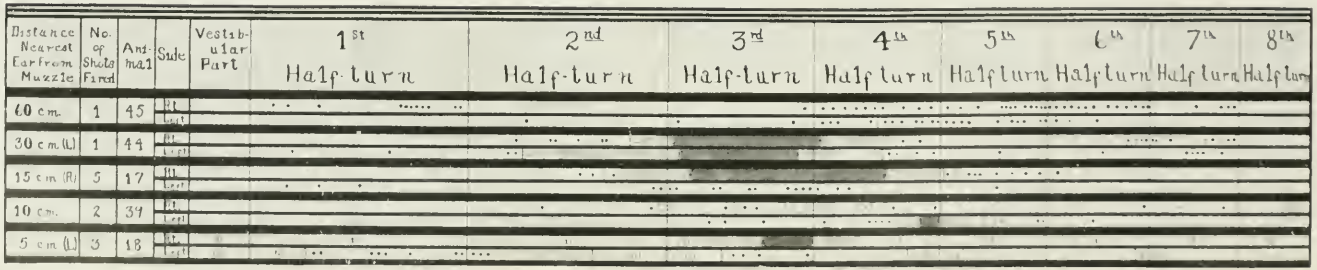

Chart IV—Plate IV.

(For description of charts see page 180.)

Legend for Plate IV

(*See pages* 178 *and* 179.)

For the explanation of the general plan of the charts and of the symbols used, see the text matter, page 159, and the preceding description of lesions. The numbers in parentheses refer to the notes given in the legends for the individual charts.

CHART I.—A graphic presentation of the condition of the organ of Corti in the cochleæ of ears which were entirely open when exposed to the detonation produced by one shot from a 45 caliber Colt automatic pistol, fired with the muzzle at 15 cm., measured from the opposite ear, the barrel pointing downward about 20 degrees from the horizontal from above and in front of the animal along the left side.

CHART II.—A graphic presentation of the condition of the organ of Corti in the cochleæ of the ears which had the open rubber ear and a glass tube, of the dimensions given in the chart for each case, placed in the usual way. With the 2.0 mm. tube, examination of the wax packing after the shooting showed the presence of wax in the end of the tube with animals 47 and 42. (Cf. Table II of the middle ear report.)

CHART III.—A graphic presentation of the condition of the organ of Corti in the cochleæ of the ears which were protected by the methods indicated. These are left cochleæ in every case, and the position of the gun was that given in the legend for Chart 1, except that the distance was measured from the protected ear.

(1) (Animal 56) The fixation of these turns is too poor for one to be certain as to possible injuries of limited extent, there are none of large extent.

(2) (Animal 53) The fixation is so poor that the sections are worthless for the determination of detonation injuries.

(3) (Animal 30) The apex of this cochlea was accidentally crushed during its removal; the resulting gross distortion is too great for one to be certain of the condition of the organ of Corti in these apical turns.

CHART IV.—A graphic presentation of the condition of the organ of Corti in the cochleæ of ears which were entirely open when exposed to detonations from a 45 caliber Colt automatic pistol with other than the usual arrangement (see legend to Chart I). The distance from the muzzle and the number of shots fired are indicated in the chart for each case. For the more exact position of the gun each time, reference may be made to Table 1 of the middle ear report.

(1) (Animal 18, right cochlea) The fixation is too poor for one to be certain of more than the general condition; there may be other areas of injury of small extent, but there are no other extensive injured zones.

(2) (Animal 18, left cochlea) This cochlea was not entirely sectioned because of poor decalcification; the areas blocked off are those not sectioned; their condition is accordingly unknown.

PUBLISHER'S NOTE.—The exact distribution of the fourth degree injury does not show clearly in these charts as printed, owing to the lack of differentiation of the intermediate and dark grays.

NOTES ON THE DECOMPOSITION OF ARSPHENAMINE*

By John B. Rieger, M.D., Boston, Mass.

COMMERCIAL arsphenamine is a mixture of dihydroxydiamino-arsenobenzenedihydrochloride, its oxidation products, mineral impurities chiefly sulphur, water, methyl alcohol and ether. Ehrlich and Bertheim[1] in 1912 dried such a mixture in a stream of carbon dioxide at 65°, and on the basis of a combustion ascribed to it the formula $C_{12}H_{14}O_2N_2As_2Cl_2$, $1CH_3OH$, the presence of the methyl alcohol being substantiated by the Mulliken and Scudder test performed on the distillate from an aqueous solution. The formula as now given in the pamphlets accompanying the drug is $C_{12}H_{14}O_2N_2As_2Cl_2$, $2H_2O$. The responsibility for the latter formula can not be stated, although Gaebel[2] as early as 1911, speaks of two molecules of water which are lost when the compound is heated in a current of dry hydrogen at 105°. The present author, having obtained a strong Mulliken and Scudder[3] test on samples of German salvarsan, American salvarsan and diarsenol, attempted a direct determination of the alkoxyl in these preparations, combining for the purpose the Zeisel,[4] Gregor,[5] and Kaufler[6] methods. The sample was dried in a current of washed carbon dioxide for two-hour periods and the alkoxyl simultaneously distilled into hydriodic acid. A pipette bent into a U served as the drying vessel and allowed the sample to be repeatedly mixed by shaking. The results are tabulated.

BRAND	WT. OF SAMPLE GM.	MG. LOSS IN WT.			MG. ALKOXYL, CALC. AS METHOXYL				% LOSS IN WT.
		65°	97°	125°	65°	97°	125°	Dist. Water	
A	0.5976	20.2	13.8	12.4	2.6	0.6	5.5	0.5	7.76
B	1.2094	26.4	20.0	10.0	4.5	3.9	2.0	8.6	4.60
C	1.2034	22.4	30.5	21.7	4.2	3.1	1.0	9.2	6.19

The progressive, though uneven loss of weight from 65° to 125°, argues against the presence of water of crystallization and suggests rather hygroscopic moisture or water of occlusion. The methyl alcohol and ether is probably held in the same way, though there is the additional possibility that part of it is chemically bound to the arsphenamine molecule as ester or ether. Since the distillation of the alkoxyl as given above, is complicated by the formation of halogenated alkyl arsenicals, the figures given can not be strictly accurate, but they show that a considerable part of the loss of weight, formerly calculated as water of crystallization, may be due to alcohol or ether.

THE QUESTION OF ESTERIFICATION

After arsphenamine has been heated for some time at 125° in the manner described, a sublimate of fine colorless needles collects in the portion of the pipette, directly above the surface of the bath, and the fetid alliaceous odor that

*From the Boston State Hospital, Psychopathic Department, Boston, Mass.

is sometimes noticeable when the ampule is first opened, becomes very strong. The crystals are very soluble in water and alcohol, give a white precipitate with silver nitrate, which turns brown and then black, and with iodine and potassium hydroxide they give a strong iodoform reaction. With ferric chloride, the same blood-red color is obtained as given by arsphenamine and o-aminophenol, but when digested with H_2SO_4-HNO_3 and reduced in the Marsh generator, the crystals give no trace of arsenic. The compound is then an ester or ether, possessing an o-amino group, and corresponds with o-anisidine hydrochloride, the crystals of which sublime undecomposed. The fetid alliaceous odor is common to arsines, and in this case seems to arise from a compound soluble in ethyl alcohol, slightly volatile in steam and very slowly reduced to metallic arsenic in the Marsh generator. In these properties it resembles most closely methyl arsenious oxide, $AsCH_3{:}O$. While it is probable that the formation of o-anisidine hydrochloride and of methyl arsine is in this case incidental to the heating process, the potentiality of a like esterification exists wherever arsphenamine, methyl alcohol, and hydrochloric acid are in admixture. During the manufacture of the hydrochloride salt, a great excess of alcohol and acid is present, and through oxidation of either the amino or the arseno group, the acidity of the R.OH is increased and the probability of esterification either during the stage of manufacture or in the ampule, is enhanced. The reactions representing these hypothetical changes are:

1. $[HCl, NH_2.C_6H_3(OH)As{:}]\ 2 + CH_3OH, HCl.$
2. $[HCl, NH_2.C_6H_3(OH).AsCH_3.]\ 2 + CH_3OH, HCl.$
3. $[HCl, NH_2.C_6H_3(OCH_3).AsCH_3.]\ 2 + O_2.$
4. $HCl, NH_2C_6H_3(OCH_3) + AsCH_3{:}O.$

OXIDATION AT THE ARSENO GROUP

The titration of arsphenamine with N/20 iodine solution,[7] is not a direct measure of the arsenic content, but is a measure of the stage of reduction of the arsenic atom, according to the equation:

$$RAs = AsR + 8I + 6H_2O = 2\ RAsH_2O_3 + 8\ HI$$

When arsphenamine is reduced with zinc and hydrochloric acid, the equation becomes:

$$2R\ As\ H_2 + 12I + 6\ H_2O = 2\ R\ As\ H_2O_3 + 12\ HI$$

Hence the percentage of arsenic calculated on this basis will always be lower than that obtained by digestion methods, and the difference must represent the percentage oxidation that the sample has suffered at the arseno group. The reaction is not reversible, as suggested by Gaebel,[8] the endpoint being constant and independent of dilution. Thus diarsenol showed 28.92 per cent arsenic by direct titration, and 30.17 per cent by Lehmann's method;[9] American salvarsan 28.70 per cent by titration and 30.10 per cent by digestion, while German salvarsan showed 29.51 per cent and 30.70 per cent, respectively. Diarsenol was therefore 1.25 per cent oxidized at the arseno group; American salvarsan, 1.40 per cent; and German salvarsan, 1.20 per cent.

OXIDATION AT THE AMINO GROUP

The amount of oxidation at the amino group may be measured by titration with sodium nitrite solution.[10] In the samples of German and American salvarsan and diarsenol examined it was found to be practically nil. In acid solution upon exposure to air there is a slow progressive oxidation to the nitro-arylarsinic acid, giving a pink color to the solution. The alkaline solution similarly exposed, and provided that the excess of alkali is not over five molecules, gradually becomes green, probably due to the formation and oxidation of an o-dihydric phenol, ammonia being freed. Arguing from the behavior of pyrocatechol and o-aminophenol, when mixtures of these are exposed to air, one molecule of the dihydric phenol in question then probably rearranges itself with one molecule of the unaltered arsphenamine base, giving upon oxidation a red solution. From this there later separates a dark red-brown precipitate, leaving a colorless supernatant fluid. This precipitate is arseniureted and is probably a phenoxazine derivative, since it is decomposed by alcoholic potash, gives a violet color with concentrated sulphuric acid, is insoluble in water and soluble in concentrated hydrochloric acid to a light red solution.

REDUCTION TO ARSPHENAMINE

Aside from the intrinsic toxicity of the impurities that may occur in commercial arsphenamine there must be considered the relative ease with which these compounds give up their arsenic. The therapeutic utility of organometallic compounds depends upon their inability to ionize, except insofar as the metal may form part of a complex anion. By thus linking the metal to carbon the characteristic oxide action is abolished and the unique effect of the molecule as a whole is obtained. There is evidence that the inability to ionize is not, for all organometallic compounds, an absolute one. Thus, sodium cacodylate, even in fresh solutions, is progressively reduced to metallic arsenic by zinc and hydrochloric acid. Arsphenamine, freshly dissolved, does not ordinarily yield more than a trace of metallic arsenic when reduced in the Marsh generator. Within an hour or two, however, especially if the solution has been alkaline, as much as 5 to 10 per cent of the arsenic may be torn from its carbon anchorage. Using exactly the same weight of zinc and hydrochloric acid, and the same amount of arsphenamine (2 mg.), the reduction is powerfully catalyzed by the solution that has stood an hour or two, whereas the fresh solution has no accelerating affect. Similarly, a zinc-platinum couple placed in a phenoxazine containing solution, brings down a heavy deposit of arsenic, whereas this does not occur in fresh solutions. One is then forced to conclude that the ability to ionize increases, the more oxygen is brought into union with the metal, and that the union of arsenic with methyl, likewise weakens the C-As linking.

REACTIONS WITH COMMERCIAL ARSPHENAMINE

The immediate action of arsenous oxide is to produce a vasoparesis, whereby there results a fall in blood pressure and exudation of fluid. On the heart, it acts like hydrocyanic acid, and according to Schmiedeberg[11] it is only

when injected into the blood stream that it causes paralysis of that organ. The symptoms of subacute and chronic poisoning are more familiar, and upon autopsy resolve themselves into fatty degeneration, chiefly of the heart, liver, and kidney. In this hospital the "nitritoid" reactions have been more numerous, since the employment of arsphenamine of other than German manufacture became necessary. From this it may be argued that the ill effects are not due to arsphenamine itself or to errors in technic, but to preformed degradation products of the base or of its congeners, which either did not exist in the German product or were there present in subliminal amount. The sample of German salvarsan examined was obtained from the Peter Bent Brigham Hospital, and represents a lot purchased since the outbreak of the war. Ormsby and Mitchell[12] state that the later importations of salvarsan were found to be distinctly more toxic than those made before the war, and as considerable doubt has been expressed concerning the source of much of this material, it is impossible to state whether the genuine German salvarsan contained combined methyl alcohol. The presence of the latter is incident to the manufacture of the hydrochloride salt, and the amount would be governed by the age of the sample and the completeness of the drying process. Neoarsphenamine may or may not contain combined methyl, since there is one process[13] of manufacture at least which does not involve the use of methyl alcohol.

PREPARATION OF ARSPHENAMINE SOLUTION

Danysz[14] regards the "nitritoid" reactions as evidence of the precipitation of arsphenamine base into the blood stream. It is true that the monosodium phenolate is precipitated by the carbon dioxide of the air, and the disodium salt is similarly precipitated after a longer time. In other words, carbonic acid is a stronger acid than arsphenamine, and will abstract sodium from the salts of the latter. While blood serum is, in a sense, a bicarbonate solution and contains free carbon dioxide, the circulating blood, if anything, functionates as a weak base. Its hydrogen-ion concentration varies directly as the ratio $H_2CO_3/NaHCO_3$, and the normal value of C_H for the human blood is given as about $10^{-7.45}$, a value that is closely adhered to in health. It is therefore difficult to see how sodium can be abstracted from the monophenolate when the latter is intravenously injected, though this may occur in the test tube. The addition of monophenolate also increases the opalescence of globulin solutions, and this also, in a sense, is a precipitation, though it is not comparable with the milkiness of some sera obtained in life from cases of late vascular degenerative syphilis. It is significant that the "nitritoid" reactions apparently occur more frequently in hospital than in private practice. In the former case the arsphenamine solution is generally made up in quantities sufficient for a dozen or more injections and the alkalized solution is allowed to stand for an hour or two. Some solutions give a garlic-like odor when freshly prepared; others, not until they have stood. This circumstance, together with the size of the dose and the idiosyncrasy of the patient determines whether a reaction will or will not be obtained. Once injected, the occurrence

of subacute or chronic symptoms is determined by the margin that exists or can be made to exist between the elimination of the drug and its reduction by the tissues.

SUMMARY

Commercial arsphenamine may contain an arseniureted methyl compound, which decomposes either in the ampule or in solution, with liberation of arsenous oxide or a cacodyl-like substance. Some preparations betray the presence of the arsine by their garlic-like odor when dissolved; others develop it only after having stood in solution for hours. According to the amount that may have accumulated, the dosage and the idiosyncrasy of the patient, a reaction marked by fall in blood pressure, dyspnea and cyanosis may occur. Once the drug has been injected, the occurrence of subacute or chronic arsenic poisoning is determined by the margin that exists or may be made to exist between its elimination and its reduction by the tissues. There is evidence that this reduction to metallic arsenic occurs too readily for safety with present commercial preparations of arsphenamine.

The work was prematurely terminated because of conditions brought on by the war, and the results are therefore not conclusive. The preparation of a neoarsphenamine without the use of methyl alcohol and a study of its therapeutic behavior would do much to prove or disprove the hypotheses advanced.

I am deeply grateful to Dr. Lawson G. Lowrey, of this hospital, for his valuable cooperation in the work.

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THE ROLE OF TUBERCULOSIS IN DEMENTIA PRECOX*

(Preliminary Study)

By H. I. Gosline, M.D., Worcester, Mass.

THE relations of the numerous forms of tuberculosis of the various organs which have proved themselves so valuable a study both from the standpoint of public health and from that of the research specialist have received little if any attention from psychiatrists since the time of Kahlbaum in 1873 (September). At the meeting of the Massachusetts Medical Society, June, 1916, it was stated in the Section on Tuberculosis that insanity, especially dementia precox, was one of the predisposing causes of tuberculosis. This was the opinion of Kahlbaum, held many years ago with regard to catatonia. At that time he pointed out, without laying any special stress upon them, the symptoms clinically known as those accompanying tuberculosis such as sweats, drowsiness, and loss of weight. He mentioned headache, and at times the bowels show diarrhea or are costive. Despite Kahlbaum's dominant interest in the intracranial findings, we find him saying that tuberculosis occurred in five of the seven cases which came to autopsy, making a percentage of 71.3. Not only has there been no advance over Kahlbaum's time in the discovery of the relationship between tuberculosis and dementia precox, but we have made little if any advance in our separation of paresis from dementia precox, in cases that are mentally on the border line. Even now, in spite of the added advantages of the Wassermann technic on blood and spinal fluid, we frequently find cases coming to autopsy with the diagnosis of dementia precox which clinically showed neurologic evidence of syphilis of the central nervous system and which at autopsy show granulations in the fourth ventricle or other incriminating evidence. As for the confusion of alcoholic cases with dementia precox we have made no advance whatever. As a matter of fact, we have turned the other way and there is a tendency today to consider alcohol as an incident in dementia precox rather than as a possible cause of the clinical picture.

With regard to the relation of tuberculosis to dementia precox, Kraepelin has made a real advance perhaps in considering that the confinement of the patient is a predisposing cause to tuberculosis rather than the tension or passive resistance of the muscles of the thorax, which was Kahlbaum's idea of the patient's predisposition to tuberculosis.

It is the purpose of the following study to establish somewhat more definitely from a statistical point of view, the relation which apparently exists between tuberculosis and dementia precox. The percentage of dementia precox cases resulting in death from tuberculosis is somewhat higher than Kahlbaum's figures when studied over a slightly longer series, and it is possible that Kahlbaum's percentage would have been somewhat larger if careful pains had been

*From the Laboratory of the Worcester State Hospital, Worcester, Mass.

Publisher's Note.—The second report of this series will appear in an early issue.

taken to rule out those cases which had an alcoholic history or which gave evidence clinically or pathologically of having suffered from syphilis.

Ruling out these cases together with those which possibly were suffering with some other infection at the time of onset of their psychosis, we have a percentage in thirty cases of 73.3 who died of tuberculosis. The percentage of dementia precox cases affected with tuberculosis should be higher than the figures show by considering merely death in dementia precox. In a great majority of the remaining percentage we will find a history of tuberculosis paralleling or antedating the history of the mental disease. The reason for the present low percentage is the obvious one, our lack of clinical methods for the discovery and early diagnosis of that most puzzling of diseases, tuberculosis. Even with the modern development of the roentgen ray in the diagnosis of pulmonary cases and with our added knowledge of the early clinical signs, our clinical methods are admittedly deficient. We no longer expect to find the tubercle bacillus in the sputum, urine or feces in order to make our diagnosis, and yet we know that many cases pass through the hands of competent physicians without recognition. Anatomically, the condition is just as difficult of accurate diagnosis. It is well known that there is difficulty in distinguishing tuberculosis from syphilis microscopically or macroscopically. The diagnosis, then, is not infrequently made wrongly, not only before death but after death. On the mental side the picture is even more confusing. We know that alcoholics may give the picture of dementia precox and that general paretics may appear like catatonics at times. Various infections may be accompanied by catatonic symptoms. There is no way from the mental picture to distinguish the cause of the disease. It is doubtless true that many more errors creep into mental diagnosis than into ordinary physical diagnosis.

Though death from dementia precox is a small matter, disability from dementia precox is a large matter. Upon the disabling factor in dementia precox rests a fair part of the necessity for large institutions for the care of the insane. In certain parts, between 75 and 90 per cent of the permanent population of these hospitals is made up of patients who have suffered from dementia precox and who are mentally incapable of carrying on an independent existence any longer.

The present study is based upon 108 cases which have come to autopsy since the institution of a permanent laboratory in this Hospital. This number is practically 8 per cent of the total number of autopsies performed in that period. The cases were thoroughly reviewed by the writer and all those discarded which gave a history of alcohol, syphilis, or infectious disease coming on at the onset of mental signs, or which gave anatomic evidence of syphilis, or which mentally might be classed under any other category than dementia precox, or in which there was some doubt as to the diagnosis in the minds of certain members of the staff. So treated, there were 63 cases of the 108 that could be promptly discarded. Tuberculosis, as a cause of death, necessarily could not save them. The one criterion as to whether they should be retained was that they should be undoubted cases of dementia precox. Fifteen cases showed special features which put them outside the pale of frank dementia precox because there might be a possibility of discussion pro and con. This left a total of 30 cases which

were retained as a basis for this study. Of this number 21 died of tuberculosis of various organs, chiefly of the lungs. One died of pulmonary abscesses from which tubercle bacilli were discovered in the smear. These 22 cases thus make a percentage of 73.3 dying of tuberculosis.

That one may have an adequate basis of knowledge of the way in which the cases were selected, a short review of the discarded cases will be attempted first. Table I is a list of discarded cases.*

TABLE I

CASE NO.	CAUSE OF DEATH	REMARKS
III-9	Retention of urine.	Granulations of IVth ventricle.
III-37	Cerebral hemorrhage.	No hallucinations or delusions.
IV-21	Edema of lungs.	Patient had fits (?).
IV-25	Lobar pneumonia. Pulmonary embolus.	Question of imbecile.
IV-37	Pulmonary tuberculosis.	Patient had fits (?).
IV-42	Pulmonary tuberculosis.	Granulations of IVth ventricle (?).
V-35	Apoplexy.	Hemorrhage at 40 years. Body tissues not examined.
V-42	Pulmonary tuberculosis.	No delusions or hallucinations (?). Patient and father alcoholic.
VI-30	Pulmonary tuberculosis.	(?) Idiot or juvenile paretic.
VI-40	Bronchopneumonia.	(?) Toxic-infection-exhaustion. Pneumonia, nephritis, diphtheria, and bronchopneumonia.
VI-41	Acute peritonitis.	(?) Idiocy. Seizures at 65 years. Old tuberculosis, intestinal ulcers (tuberculosis or cancer?).
VI-62	Enterocolitis. Vegetative endocarditis.	(?) Infection-exhaustion. Acute onset at 54 (10 to 20 days), (?) nephritis, old tuberculosis.
VII-1	Pulmonary tuberculosis, enterocolitis.	Alcohol and polyuria.
VII-9	Pulmonary, intestinal, laryngeal tuberculosis.	Maniacal, prostitute, alcohol (?), lues (?).
VIII-15	Suicide by hanging.	Psychopath (?), manic depressive (?), hysteriform tantrums, freudian complex (?), fits at 7 or 8. Old tuberculosis, cystic ovaries.
IX-2	Bronchopneumonia.	"Chronic mania" (?), manic depressive, tantrums, suggestible. Pulmonary tuberculosis.
IX-19	Acute miliary tuberculosis. (First called sarcoma bronchial glands.)	Syphilis with secondaries. Absent k. j., pupils stiff to accommodation, (?). Babinski; no hallucinations.
IX-31	Heart failure.	No hallucinations or delusions, three attacks. Rales, markedly costive. Old pleurisy.
IX-82	Pulmonary and intestinal tuberculosis.	Two attacks. (?) history of lues. One child, one miscarriage.
X-9	Tuberculous enteritis.	(?) Imbecile. Moderate alcohol. Old tuberculosis.
X-10	"Cardiac incompensation."	Suicidal. Fear affect. Old tuberculosis.
X-20	Dermoid cyst with carcinoma (hemorrhage).	Fear affect. Some alcohol.
X-49	Heart disease.	No delusions. Autopsy incomplete.
X-76	Heart failure.	Onset at 63. "Depressive delirium." (?) Presenile. Old pleurisy.
XI-15	Sarcoma of jaw.	(?) Alcohol and syphilis. Pulmonary tuberculosis.

*The question of mistaken diagnosis does not enter here. These cases were not suitable for this study for reasons which will be apparent.

TABLE I—(CONTINUED)

CASE NO.	CAUSE OF DEATH	REMARKS
XI-25	Duodenal perforation and peritonitis.	Patient claims delirium tremens.
XI-30	Uremic convulsions.	No history. "Hysteriform seizures." Admits exposure. Neurologic signs.
XI-44	Pernicious anemia.	(?) Freudian. 1st husband luetic? Operation "erosion of womb" (?), pulmonary tuberculosis. Pleural effusion.
XI-52	Basilar meningitis.	Onset at 50. Alcohol. "Crazy after men." "Faints." Clinical t. b. Previous typhus.
XIII-4	Broncho- and lobar pneumonia.	Autopsy incomplete.
XIV-17	Acute pulmonary edema. (Cardiac dilatation.)	(?) Epileptic imbecile. 9 attacks. 1. Acute mania following grippe. 2. Secondary dementia. 3. Recurrent melancholia. 4. Recurrent melancholia (manic). Alcoholic.
XIV-42	Acute dilatation of heart. Acute hemorrhagic pancreatitis.	(?) Infection. Acute mania. Convulsions.
XV-6	Ruptured heart.	Incomplete history. Tuberculosis at apex.
XV-22	General peritonitis.	"Tubes reddened." Acute, following tonsillitis. Apical scars, double plastic pleurisy.
XV-50	Chronic colitis.	Onset at 42. (?) Manic depressive, atypical. Old pleurisy. Pupils unequal, postmortem.
XV-58	Acute colitis.	"Fantastic paranoia." "Paranoid condition" (?) Imbecile. Followed injury. Alcoholic.
XV-67	Acute colitis.	No past history.
XV-74	Exhaustion.	Autopsy incomplete.
XV-79	Gangrene. Cellulitis.	(?) Manic depressive. (?) Paresis. Admits exposure. Alcohol. K. j. and pupils unequal. Granulations, IVth ventricle. Old tuberculosis.
XV-84	Pulmonary and intestinal tuberculosis.	Alcohol. (?) Lues.
XVI-37	Chronic valvular endocarditis. Anasarca.	Immoral. Glands enlarged. Alcohol. K. j. diminished.
XVII-4	Miliary tuberculosis.	No history. No notes 1902-1911.
XVII-16	Multiple abscesses.	Syphilis. Alcohol.
XVII-25	Chronic nephritis (pyelo-). Edema of lungs.	(?) Constitutional inferior. Some "drink."
XVII-40	Abdominal carcinosis.	(?) Constitutional inferior. No delusions or hallucinations. Alcohol. Admits exposure. Old pleurisy.
XVII-74	Bronchopneumonia.	(?) Paranoid condition in constitutional inferior. (?) Syphilis. Old pleurisy.
13-3	Lobar pneumonia.	(?) Constitutional inferior. No hallucinations. Onset at menopause at 42. Apical scars.
13-10	Aneurysmal dilation of heart Pulmonary infarct and edema.	(?) Syphilitic paranoid condition. Moderate alcohol. Granulations IVth ventricle.
13-31	Acute pancreatitis (?). Fat necrosis. Cholelithiasis.	Onset at 40. (?) Septic or tuberculosis temperature.
13-35	Cardiac aneurysm. Coronary sclerosis.	(?) Infection-Exhaustion. Adhesive pericarditis. Apical scars.
13-40	Septic decubiti. Abscess of lung. Vegetative endocarditis.	"Coincident with muscular rheumatism." Onset at 52.
13-46	Acute enteritis. Early peritonitis.	Syphilis with secondaries.
14-8	Decubiti. Septicemia (?).	Tuberculosis temperature. Absent knee jerks. Some pleural adhesions. Sclerosis of posterior columns.
14-21	Suicide by hanging.	(?) Psychopath with manic depressive. Pulmonary tuberculosis.

TABLE I—(CONTINUED)

CASE NO.	CAUSE OF DEATH	REMARKS
14-27	Postoperative plastic peritonitis. Carcinoma sigmoid with intestinal obstruction.	(?) Defective. Old pleurisy.
1915.6	Pulmonary tuberculosis.	(?) Cerebrospinal syphilis. Blood positive, spinal fluid doubtful. Tuberculosis in sputum.
1915.21	Bronchopneumonia. Pellagra.	(?) Defective. W. R. Blood doubtful, then negative. Gumma of liver (?). Apical scar.
1915.29	Bronchopneumonia.	One faint. (?) Prostitute. Old pleurisy and "latent" tuberculosis.
1915.40	Acute hemorrhagic pancreatitis. Sclerosis and constriction left coronary with thrombus.	Alcohol.
1915.45	Pellagra.	Alcohol. (?) Lues. Wife had miscarriages.
1916.29	Lobar pneumonia. Parenchymatous nephritis.	Onset at 53. No hallucinations. Old pleurisy.
1916.30	Carcinoma sigmoid and rectum.	(?) Toxic-exhaustion.
1916.32	Catalepsy.	Temperature. Influenza in sputum and blood (taken at autopsy).

A brief summary will reveal certain clinical and certain pathologic data on which these cases are dismissed. Of the clinical reasons are the fact of absence of hallucinations or delusions in certain cases, the presence of convulsive seizures, the question of imbecility, constitutional inferiority, psychopathic personality, manic depressive insanity, alcoholic psychosis, syphilitic history or other evidence of syphilis, or the presence of certain other factors of a toxic, infectious, or exhaustive nature. On the pathologic side the factors are granulations of the IVth ventricle, cerebral hemorrhage at the age of forty, adhesive pericarditis, and question of gumma of the liver. A few cases had incomplete records.

It will be noted that there is frequently a history of tuberculosis in these patients and some died of the disease but this has not been used as a reason for retaining cases.

Table II is a list of the cases retained.

TABLE II

CASE NO.	CAUSE OF DEATH	REMARKS
II-31	Deglutition pneumonia	Pleural cavities obliterated. Left upper lobe, radiating scar and bronchiectatic cavities.
III-6	Gangrene of lungs.	(?) Tuberculous. Old tubercles at apex.
III-14	Pulmonary tuberculosis.	
III-24	Pulmonary tuberculosis.	
III-31	Pulmonary tuberculosis.	
III-43	Pulmonary tuberculosis.	Tuberculosis of liver and kidneys.
IV-8	Pulmonary tuberculosis.	
IV-16	Pulmonary tuberculosis.	
IV-18	Pulmonary tuberculosis.	
IV-47	Tuberculosis of lungs, liver, kidneys, spleen.	
V-3	Pulmonary tuberculosis (tuberculous pneumonia).	
V-39	Pneumonia.	Clinically and anatomically tuberculosis.

TABLE II—(CONTINUED)

CASE NO.	CAUSE OF DEATH	REMARKS
VI-33	Cancer of duodenum.	Liver affected. Death at 31. Clinically tuberculosis and anatomically tuberculosis of lungs. Father and mother died of tuberculosis.
VII-25	Endocarditis.	Old tuberculosis anatomically.
VII-41	Pulmonary tuberculosis.	Hemorrhages. (?) Tubercles of pia.
VII-46	Pulmonary and intestinal tuberculosis.	Positive sputum. Albumin and casts.
VIII-3	Pulmonary tuberculosis.	
X-21	Bronchopneumonia.	(?) Old tuberculosis.
XII-28	Tuberculosis and mitral insufficiency.	Acute course of 10 days' duration.
XIII-17	Pulmonary tuberculosis.	Rapid course.
XVI-22	Lobar pneumonia (pneumococcus meningitis).	Old pleurisy and pulmonary tuberculosis.
XVI-23	Pulmonary tuberculosis.	
XVII-43	Tuberculous intestinal ulcers. Acute degenerative nephritis.	Old pulmonary tuberculosis. "Frontal encephalitis."
XVII-57	Typhoid fever. Gangrenous cellulitis, pelvis.	Old pleurisy. Apical scars.
14-7	Abscesses of lung.	Smear from abscess positive for tuberculosis.
1915.18	Pulmonary and intestinal tuberculosis. Acute vegetative endocarditis.	
1915.25	Fibroid phthisis. Chronic interstitial nephritis.	
1916.25	Tuberculosis, ileum, etc.	Solitary tubercle brain and cerebellum.
1916.36	Double lobar pneumonia.	Old pleurisy.
1916.37	Chronic interstitial myocarditis.	Old pleurisy. (?) Tubercle of spleen.

Certain of these cases show a remarkably intimate connection between the course of their physical disease, tuberculosis, and the course of their psychic disturbance. This type of case has been described by Claude and Rose[1] and by them has been considered in the group of Toxic-Infection Psychoses. The number of cases in the present study which resemble that of the French writers is seventeen. These will receive special attention in a separate study. It is fitting that they should be considered in the present group of dementia precox cases until such time as they shall receive proper recognition as belonging to the toxic-infectious group.

Doubtless the dementia precox group will in the future be further split up on the physical side, as the start has already been made in splitting off paresis and those cases of an infectious origin. But the psychic complex can never be split into anything but its psychologic elements or possibly, its psychopathologic elements. It must not be forgotten that cases of paresis which appear like dementia precox are, on the psychic side, really dementia precox, though the physical cause is the process caused by the spirochete. It is already admitted that alcoholic cases of a certain type may simulate paresis, as the time-honored name alcoholic pseudoparesis bears witness. The necessary basis for the similar pictures is not the causative agent, but is the location of the pathologic process.

The ideas outlined above with regard to paresis and alcoholic pseudoparesis may apparently be applied also to dementia precox and may prove to be of more than passing significance. The work of Southard[2] on the relation which

exists anatomically between the catatonic form of dementia precox and parietal lobe lesions and between the paranoid form and frontal lobe lesions, independently of the causative or accompanying physical factors, furnishes us the necessary anatomic substrate.

The time-worn question as to why all cases affected with our supposed causative agent do not give us the mental disease has no longer any logical value since the discovery of the cause of paresis. It is now recognized that this is another question in quite a different field and need not concern us here.

The question next arises as to the reasons for considering tuberculosis as a causative factor in the cases upon which this study is based. It has already been said that seventeen cases showed the mental disease to be so nearly parallel to the physical that they will be given separate consideration with a similar case published in the French literature. It will suffice here to give the age of onset, age at admission, and age at death in these cases and to describe more at length the other thirteen cases whose course did not parallel so succinctly the physical disease.

In Table III are given seventeen cases with age at onset, etc.

Table III

CASE NO.	AGE AT ONSET	AGE AT ADMISSION	AGE AT DEATH
III-6,	46	47	48
III-14	18	21	23
III-24	31	31	32
III-31	39	39	40
III-43	25	25	27
IV-8	19	19	20
IV-16	26	27	28
IV-18	22	22	23
V-3	23	24	25
VII-41	24	24	27
VIII-3	44	45	45
XII-28	19	20	20
XIII-17	18	18	19
XVI-23	25	29	29
XVII-43	33	34	34
14-7	28	28	29
1916.25	24	26	29

The striking thing in this series as it stands is the short duration from onset to exit. Another incident of interest is the predominance of the third decade cases, the decade from twenty to thirty. It seems that we may at some future time be able to split off such cases from the total group of dementia precox in some such way as that suggested in the article by the French writers mentioned above.

Comparing this table with the causes of death mentioned in Table II, we find that all but one died of tuberculosis and the cause of death in that one (Case III-6, gangrene of lungs) may be suspected to be in some way linked with tuberculosis since there were tubercles at the apex. One case (XII-28) was complicated by mitral insufficiency. Two had tuberculosis of other organs than the lungs as cause of death (XVII-43, 1916.25) and one died of abscesses of

the lungs in the smear of which tubercle bacilli were found. These few facts will serve in a rough way to indicate the close connection with tuberculosis which exists in these cases.

Let us next approach those cases in which the connection is not so clear cut. In these cases the ages at onset and at admission are frequently separated and perhaps more frequently the ages at admission and at death are far apart. These are the mild cases which stay in the community until the relatives can no longer care for them or the cases which enter the hospitals with an acute attack of mental trouble from which they recover but with residuals which incapacitate them for further independent existence in the community.

The age at onset, etc., in these cases is given in Table IV.

TABLE IV

CASE NO.	AGE AT ONSET	AGE AT ADMISSION	AGE AT DEATH
II-31	33	43	76
IV-47	29	60	61
V-39	25	32	74
VI-33	26	26	31
VII-25	22 (?)	35	53
VII-46	27	27	34
X-21	22	22	23
XVI-22	29	30	50
XVII-57	25	26	29
1915.18	44 (?)	45 & 49	57
1915.25	(?)—"Years"	48	49
1916.36	25	27 & 31	54
1916.37	28	31	65

Comparing Table II, the causes of death will be found to be varied, as they would be expected to be in recovered cases. They are pneumonia (II-31, V-39, X-21, XVI-22, 1916.36), tuberculosis (IV-47, VII-46, 1915.18, 1915.25), cancer of the duodenum (VI-33), cardiac disease (VII-25, 1916.37), and typhoid fever (XVII-57). But in all these cases there was clinical evidence in the feeling of weakness on the part of the patient, or the variations in weight, or in the temperature chart, or at autopsy there was anatomic evidence of the presence of tuberculosis, or of its previous existence. This evidence, linked with the course of the mental symptoms in these cases, gives a view of the relationship which is as clear as any which can be obtained by present-day methods short of the actual demonstration of organisms or of their products in cases such as this paper has outlined. That such demonstration of organisms and their products may now be possible is a matter for the future. Certainly the method of Petroff[3] for the cultivation of the tubercle bacillus from body tissues and the complement-fixation test as practiced by Bronfenbrenner and others[4] for tuberculosis should be tried in these selected cases. It is not to be hoped or expected that such tests and examinations will show any high percentage of positives in random or routine examinations of dementia precox cases. This on the theory that dementia precox is a mental symptom-complex which depends for its existence upon the difference in function of brain areas which are topographically distinct. The cases selected must be those of tuberculosis, if the tests are to be positive. That there is a certain residue of dementia precox

CASE II-31*

PHYSICAL	MENTAL	SUMMARY
1878-'79 — Abnormal appetite with vomiting begins and continues till the end.	1864—Insane 10 years. Excited, violent, shy, suspicious, then seclusive. 1865—"Disinclined to exertion." 1868—Violent at times. 1871—Nervous and excitable. 1876—"Can remember things done in a former existence," seclusive. 1879-'79—More sociable. "Catholic priest comes into his room at night and makes him vomit." Writes much incoherently. 1881—"Visions." Talks to self. 1884—Visions of the dead. Noisy at night. 1886—Denies having relatives. 1887—Bothered by devils and spirits. 1888—Undresses in daytime. Prescribes for imaginary patients. "Imps fly into room and drop arsenic into food." 1889—Talks, laughs and sings to self in room. "Prussic acid put through window by enemies." 1891—Put meat and water in bottle and took "vile mixture." Goes out after refusing for five years. Says he is a ghost murdered 30 years ago. 1894—Disoriented.	Insane 10 years. Active on admission. Thirteen years, dull with active periods. Then deluded. Two years later, abnormal appetite and vomiting which continued. Three years later, visual hallucinations. Progressively more active with more profound disintegration of the personality. Autopsy reveals distended ileum and large redundant colon. Old pleurisy and pulmonary tuberculosis. Fresh bronchiectatic cavities. Chronic nephritis. Vessels atheromatous.

*In the Conduct Charts: × means that the sign was present every day or nearly every day of the month. ± means that the sign occurred many times during the month. | means that the sign occurred but once during the month.

cases in the causation of which tuberculosis plays a part, is the theme of this paper.

The cases are presented in chart form as being the easiest way in which to correlate mental and physical events.

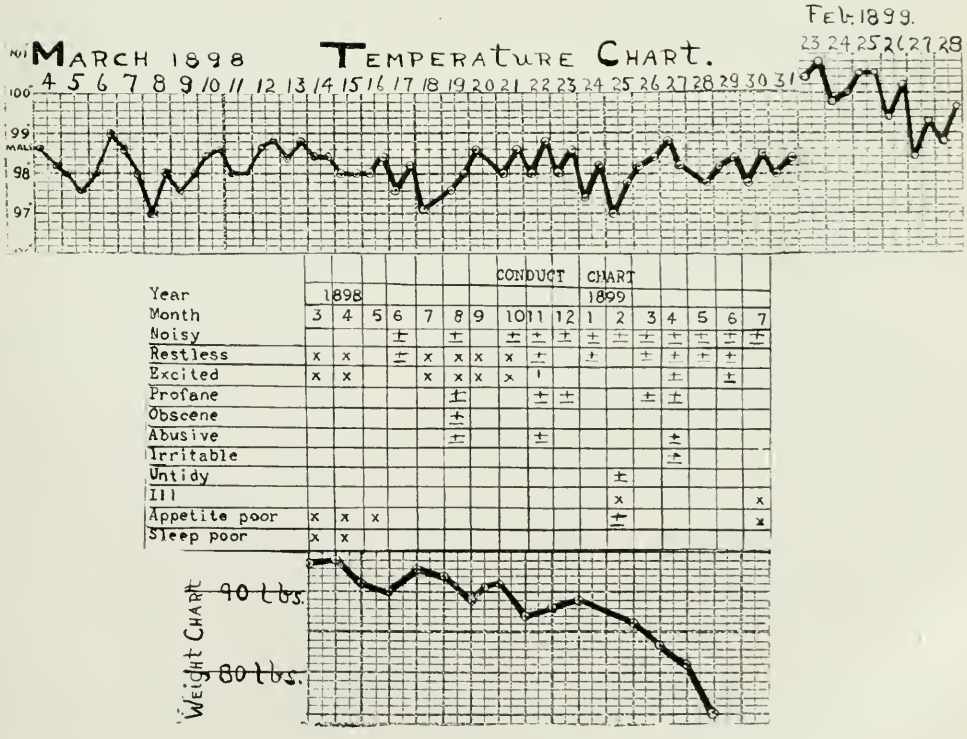
CASE II-31.—It is obviously impossible to judge the age of old adhesions or of quiescent tuberculous processes and hence impossible to assume any connection between those old processes found in this case and the mental history extending back over twenty-eight years. No one will deny that the connection is possible since we know that a tuberculous process may be latent or subacute for many years, but many will think that the connection is unlikely. Perhaps the active lighting up of the mental process in the last three years of life will be allowed to be in some way dependent upon the process which led to the formation of the fresh bronchiectatic cavities found at autopsy.

CASE IV-47.—This case is similar to the above in the long duration and character of the disease, lasting thirty years with active episodes and finally running a terminal course of activity. At autopsy there were active and latent tuberculosis with tubercles in the liver, kidneys and spleen. With the late active course there was weakness, downward tendency of the weight, and unexplained temperatures which were suggestive of tuberculosis in places.

CASE V-39.—A history of exposure to tuberculosis is followed by active mental symptoms which soon lead to dementia while on the physical side there is chronic bronchitis with asthma. A morning and afternoon temperature kept for two years gives fair evidence of the tuberculous nature of the patient's physical

CASE IV-47

PHYSICAL	MENTAL	SUMMARY
March, 1898—Numerous, depressed, nonpigmented scars in skin. Reflexes exaggerated. Tremor of hands and tongue. Urine negative. "Feels weak." April, 1898—Insomnia. Feb., 1899—Temperature, lungs negative. Untidy. March, 1899—"Has a cold." June, 1899—Sits with feet in chair and hands on head. July, 1899—Lungs negative. Albumin present in urine. July 20 (next day), slight dullness at left base, posteriorly. Diarrhea. Too weak to walk. Temperature 97.8° to 102.2°, pulse 75 to 134, respiration 19 to 42. July 22, 1899—Died.	1866—Onset with delusions of losing property. Collected old tin cans, etc., into her room. Talkative. Woke nights, screaming. Careless. 1866-1898—Gradual silliness, childishness, "temper" by breaking dishes. Muttering, 1888-1898. 1897—Wandered away and said her folks were dead. 1898—Went to a stranger's house and ordered them out. Let herself out of window with rope at midnight, ordered stranger out of his house again and hid in his orchard. Disoriented for time, place, person. Says she is 23 years old. Irrelevant, obscene, silly, disconnected speech. Auditory hallucinations. Abusive, profane, restless, excited, noisy, violent. Cries and tries to escape. Irritable and seclusive. 1899—Resistive. April—Aggressive.	Onset at 29 with delusions and active episodes, gradually becoming feeble-minded over the next thirty years. At 60 conduct and speech become active and remain so till death at 61. Physically there is great "weakness," insomnia, unexplained temperature and a "cold." Autopsy shows apical adhesions. Nodules in right and left lungs, some encapsulated and hard, some with soft, caseous centers. The liver is "peppered" with small gray-white spots. Nodules in kidneys and spleen. CASE IV-16



CASE V-39

PHYSICAL	MENTAL	SUMMARY
Husband died of tuberculosis. 1879—Pain in chest when heart is weak. Feet swollen. Chronic bronchitis. Chronic gastroduodenal catarrh with jaundice. 1887—Chronic bronchial trouble. Acute exacerbation later. 1892—Remains in bed. Asthma. 1897, Oct. 29—Habit scoliosis, emaciated, diminished expansion, dull right base posteriorly and crackling rales. Apices hyperresonant. Knee-jerks diminished. Dec. 3—Dullness right anterior. Breathing rough left and bronchial right. 1898, June 2—Sputum negative for tuberculosis.	At 25, after childbirth, excited, threatening, restless, jealous, religious. 1858—Boston Lunatic Hospital. Mania with delusions. 1879—Worcester State Hospital. Demented. 1885—Discharged, unimproved. 1887—Admitted, melancholy. Notices attentions of nurses later. 1892—Fails to notice attentions. 1896—Groans when spoken to. 1898—Quiet. Says "many thanks" for each attention of the nurse.	History of exposure to tuberculosis. Active onset at 25 and at admission, age 32. Demented at 53 and showing chronic bronchial trouble which is called asthma at 66. Lung signs and dementia increase till death at 74. Autopsy shows distended cecum and rest of colon shrunken. Adhesions over right upper lobe externally and posteriorly and lower lobe externally, posteriorly and to diaphragm. Lower one-half of right lower lobe solid, blue-gray, and studded with gray nodules. Scars at apex of left lung and inferior part of lower lobe solid, bluish and nodular.

Year	1897	1898												1899											1900			
Month	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4
Untidy	x	x	x																										
Ill	x	x	x		x	x	x	x	x		x	x	x	x	x	xx		x	x	x	x	x	x	x	x	x	x	x	x
Appetite poor	x	x			x	x	x	x	x		±	x	x	x	x	x	x			±	x	x	x	x		x	x		
Sleep poor							x									±	±	±	x	x	x	±	x	x					

No weight chart—patient too weak. (See Temperature Charts, pages 197 and 198.)

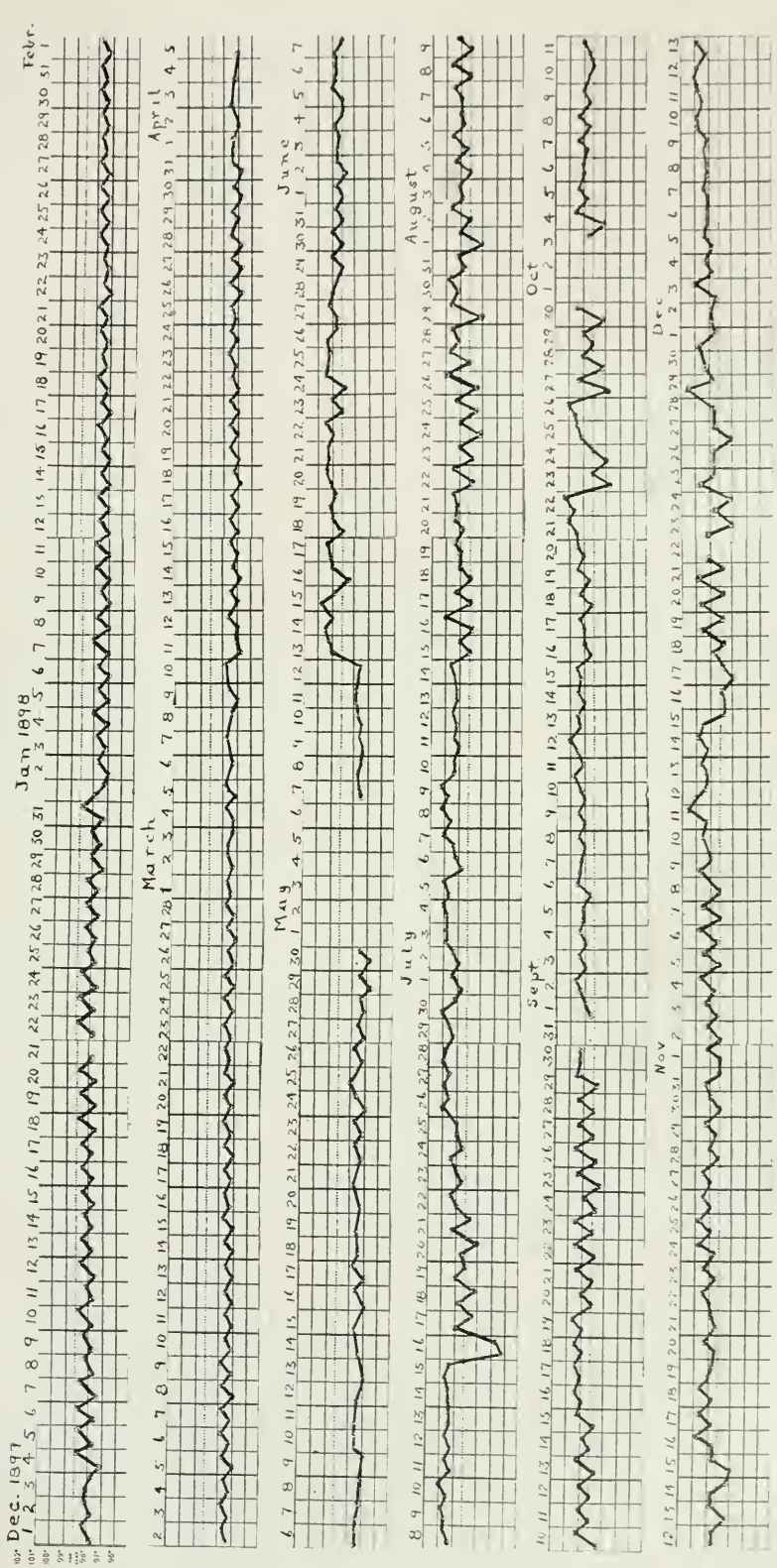
trouble. Autopsy confirms the suspicion with signs of chronic and of terminal acute tuberculosis.

CASE VI-33.—Exposure to tuberculosis is followed by mental symptoms and physical signs such as a feeling of exhaustion, anemia and poor state of nutrition. Patient dies following hemorrhage from an ulcer of the duodenum thought to be cancerous. Death at thirty-one. There were old pleurisy and nodules in the lungs, difficult to differentiate the nodules as tuberculosis or as cancerous metastases. The shape of the chest suggests pleurisy, or even an old empyema or plain effusion. The weight chart suggests an independent, metabolic disorder (but not of endocrine origin) and this parallels the noisiness and restlessness of the patient. The temperature chart sufficiently explains the nature of the patient's weakness and the total case casts doubt upon the cancerous nature of the duodenal lesion.

CASE VII-25.—Sudden onset with slow course extending over thirty years and showing two distinct active episodes. Terminal nephritis but without mental reaction. Old pleurisy and pulmonary tuberculosis. Absence of active tuberculous lesions. Following last active period a remarkable increase in weight during which mental signs were subsident.

CASE VII-46.—Sudden onset with active symptoms which continue with slight change till the end. Duration seven years. No physical notes till sixth

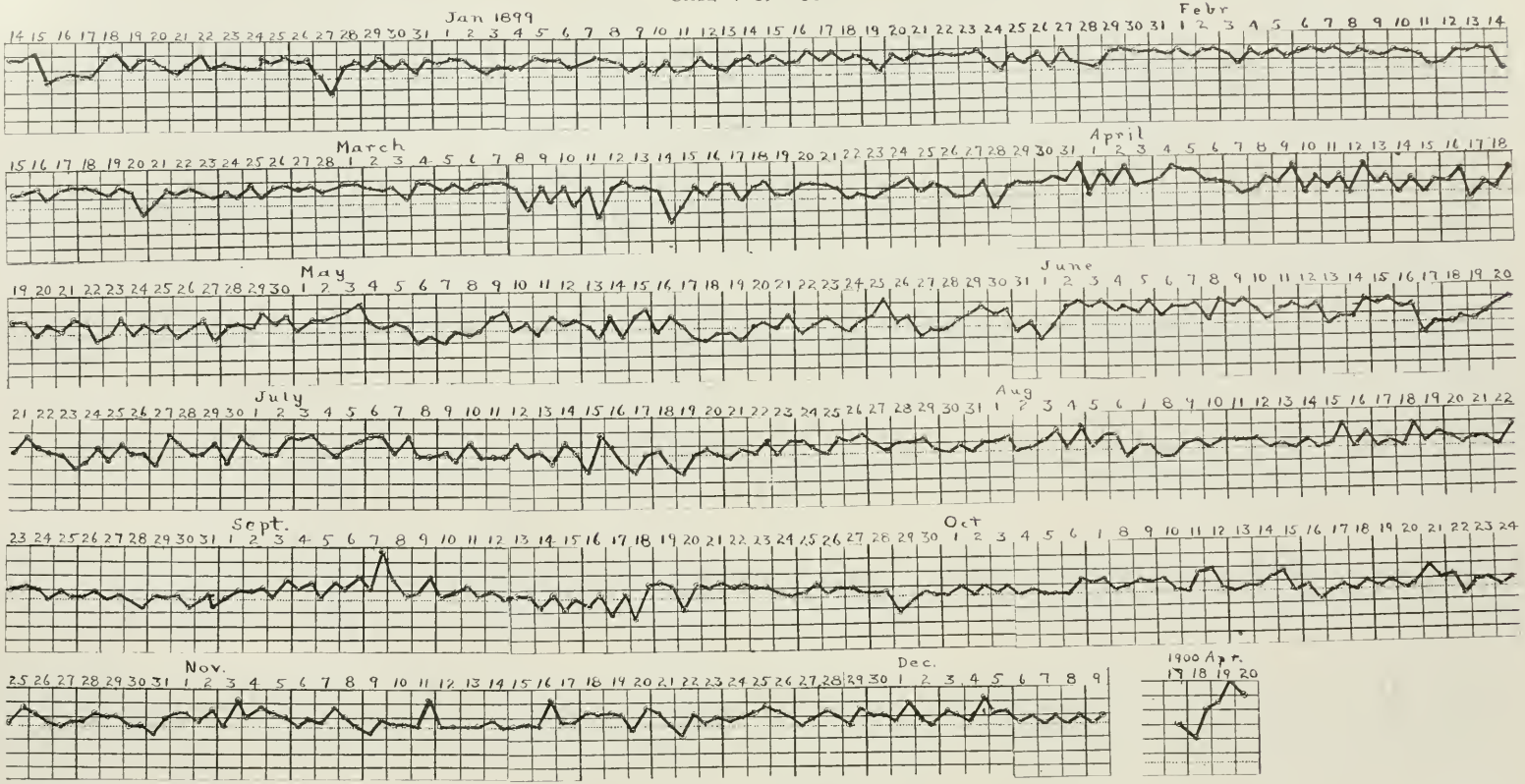
CASE V-39



(See Table, page 196.)

(Chart continued on page 198.)

CASE V-39—CONT'D



(See Table, page 196.)

year when weight falls, a typical temperature is noted, and the mental activities on the conduct side increase. Autopsy showed old pleurisy, pus cavities and tubercles in the lungs, tuberculous ulcers of the ileum and cecum, and free fluid in the chest and abdominal cavities.

Case X-21.—A sudden onset with active physical and mental symptoms ends in death in one year. This case resembles the French case in the main but lacks so positive proof of the presence of tuberculosis. At autopsy there were abundant pleural adhesions. There was atheroma of the aorta. Changes of this nature in the arteries are frequent even in early cases of dementia precox.

Case XVI-22.—An active onset of short duration is followed by fourteen years of comparative inactivity and six years without active mental symptoms. The weight shows no general upward or downward tendencies though there are occasional transient variations. Autopsy shows extensive, old pleurisy and an encapsulated, caseous mass with several tubercles in relation to an old apical scar. The history of the last six years is rather inadequate, but it would seem that the encapsulated mass should have some effect on the organism unless the amount of absorption from it were very small. The slight variations in weight, mentioned above, show a fairly close connection with disturbed periods. One might imagine that there was some connection between these periods of weight loss and mental disturbance and the periodic poisoning of the organism by some hidden focus, but it would be asking too much to expect one to believe it.

Case XVII-57.—Acute onset with mild, active symptoms and headache is shortly followed by weakness and tuberculous temperature. Death in three years with symptoms unabated. Weight seems independent of mental state. Tuberculosis of the lungs completes a picture very similar to the French case but not included there because death was due to typhoid.

Case 1915.18.—Gradual onset with remissions. Weak from the beginning. The weight drops, then the appetite fails. A moderate afternoon rise in temperature accompanies the fall in weight. Variations in temperature regularly accompany the changes in conduct, the refusal to work and the loss of appetite. It is to be regretted that the weight chart is incomplete. Pulmonary signs develop long after the weight and temperature charts are practically pathognomonic. Autopsy reveals pleurisy, tuberculous pulmonary abscesses, and tuberculous ulcers of the ileum.

Case 1915.25.—A mild course of many years terminating with active symptoms of one year's duration. Weight drops, temperature is suggestive. Lungs give evidence of tuberculous process of long duration with old pleurisy and final tuberculous pneumonia.

Case 1916.36.—Onset gradual, symptoms constant but of low grade for many years. Pleural adhesions of moderate extent. Though the weight dropped somewhat and the temperature is slightly suggestive, the physical picture is incomplete on the whole. The symptoms were mild corresponding to the slight changes at autopsy. The patient's homicidal attempt was apparently due to the content of his hallucinations rather than to his own heightened activities.

Case 1916.37.—A long, chronic mental disease ends with vascular trouble.

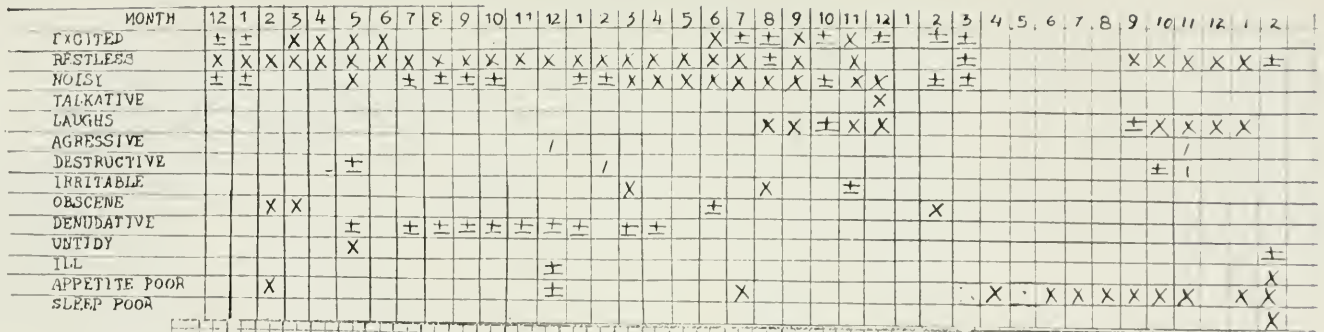
CASE VI-33

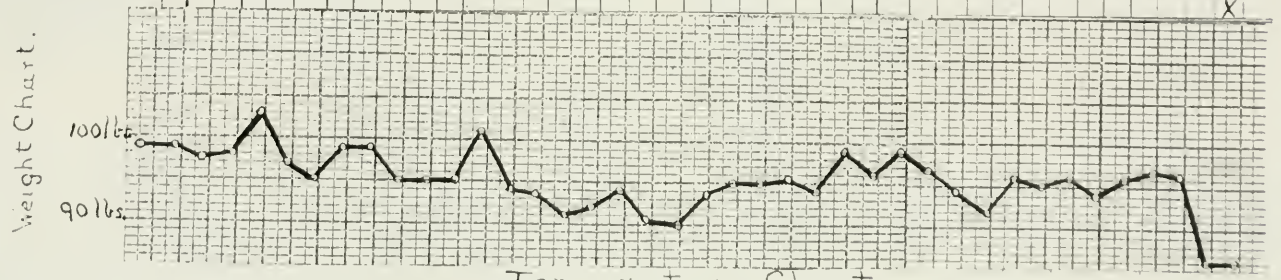
PHYSICAL	MENTAL	SUMMARY
Father died of tuberculosis at 30. Mother died of hemorrhage of the lungs when young. 1896, May-June — Had a "nervous shock," i. e., grew dizzy, faint, shivered and was cold, then felt exhausted and weak. Summer—Complained of headache much. On visit gained appetite and flesh. December — Insomnia and poor appetite. P. E.—Poorly nourished, skin anemic, feels tired, headache all over and in her eyes, knee jerks slightly exaggerated. Right chest, low, is prominent, and posteriorly projects forward. Left chest small anteriorly, depressed below, prominent posteriorly. Scoliosis, lower dorsal, to left and upper, compensatory to right. Right base dull. Periods irregular. 1901, January—In bed, no complaint but weakness. (See temperature chart.) February—Fainted when getting out of bed. Ten hours later, passed liquid blood and clots by rectum. Reds, 1,512,000. Whites, 35,700. Hb., 15%. Later, tumor in right upper quadrant. Sputum negative for tuberculosis.	1896. December — Dull, depressed, immodest, staring. Thought she did things mechanically without "feeling" what she was doing. Admitted—confused, hallucinated (auditory), disoriented for time and place, recent and remote memory good, talkative, "food and medicine" poisoned, suspicious, "people in her room." 1897. January—"Food tastes strangely." April — Theatrical and constrained in her movements. Fails to recognize friends. Kisses everyone. May—Rhyming. June—Exhilarated, silly. November—Dances and kicks. 1898, July—"Electricity in the air works on her nerves and makes her dance." Appearance careless. 1899, June—Strikes stomach and head with fist, pulls her own hair. 1900, May—Untidy in every way.	Sudden onset with physical symptoms at 26. Mental signs 6 months later. Exposed to tuberculosis. Signs in lungs and shape of chest. Mental signs more active for three years. One year later, exhaustion, profound anemia and death at 31. Autopsy—Hair tinged with gray. Transverse colon at pubes. Duodenum a hard, nodular mass with soft areas; attached to kidney, to hepatic flexure by old, dense adhesions, and to gall bladder. Adhesions right lung, externally, left lung, posteriorly except apex and to diaphragm. Right middle lobe contains soft, flat, solid bodies from which a milky, thick juice may be scraped. Nodules in surface and substance of liver, whitish milky, thick fluid and "cheesy" plugs. Center of one completely "cheesy." Second part of duodenum seat of deep ulcer. Edges thick, dense, pork-like; walls pale gray. Tissue necrotic with many fibrous strands. Necrotic material yellow-gray. Right kidney cystic, calculi. Calcified plaques in pia.

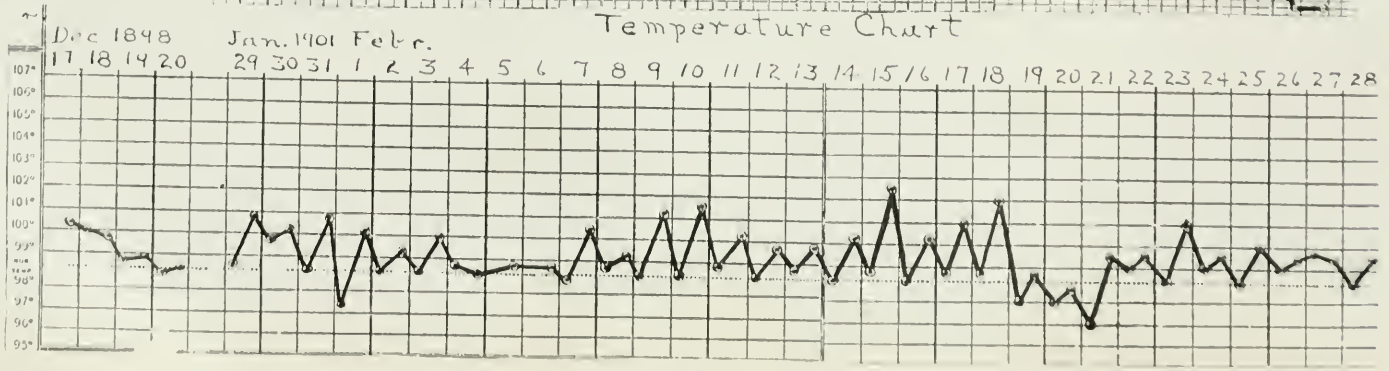
(See Chart, page 201.)

CASE VI-33

Conduct Chart







(See Table, page 200.)

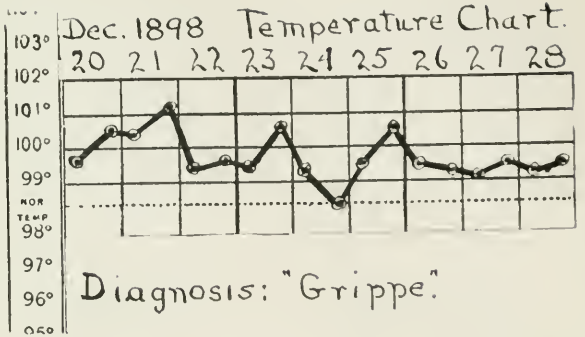
Case VII-25

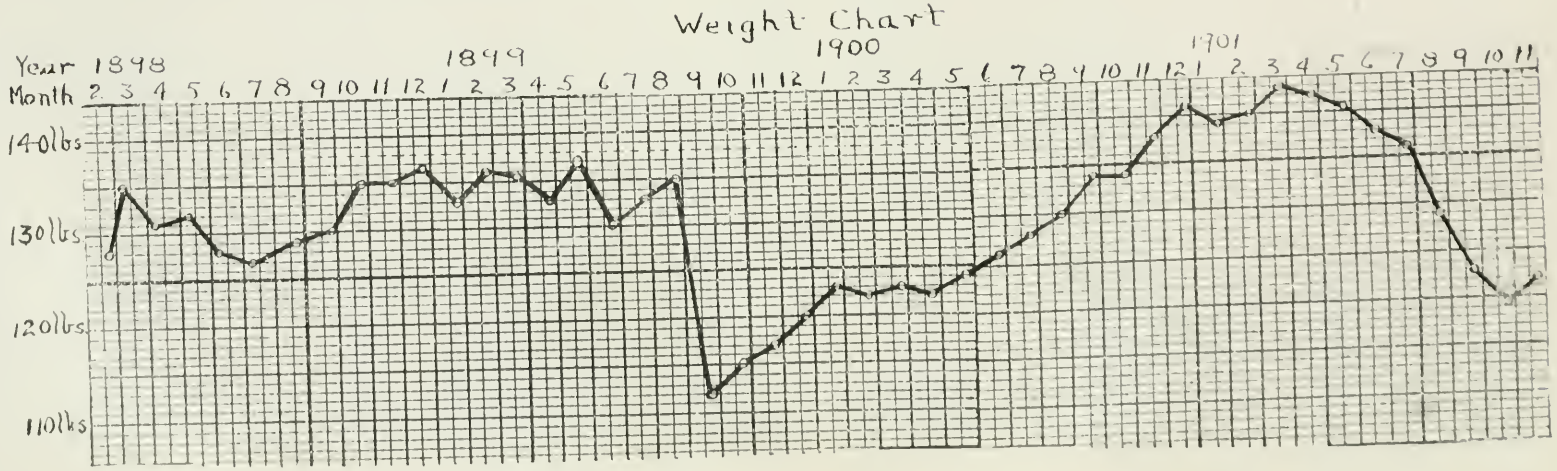
PHYSICAL	MENTAL	SUMMARY
1898, Dec.—"Grippe." 1901, Dec. 14—Considerable albumin, numerous granular and few epithelial casts. Dec. 21—Albumin moderate, epithelial, hyaline and granular casts. Dec. 26—No albumin, few epithelial, many hyaline and granular casts. Leucocytes, 8,500. Chill before temperature but malaria not in blood. Dec.-Jan., '01-'02 — Four hourly "septic chart."	1870 (?)—Shortly after marriage, jumped out of window and ran into swamp. 1884—Admission. "A ring regulates her mind." Food poisoned. Things filled with electricity. Snakes in her bed. Conversation disconnected. Talks to self. More excited during menses. 1887—Incoherent. 1889—Sits about, picking face. 1895—Face sore from picking. 1896—Talks to self. 1898—"Fleas bite her," so she picks. Assumes attitudes and stares. 1899—Scolds, laughs, talks. Does not want to be observed—talks rapidly, without noticing question, when addressed. 1901—Never converses; answers monosyllabic. Feb., 1898—Denudative 2 days. April, 1898—Noisy 1 day.	Sudden onset at about 22. After 13 years, admitted with delusions, incoherency. Self-mutilation after 5 years. Ten years later, active episodes. Two years later, dull, demented, signs of nephritis. Death. Autopsy—Omentum adherent, right iliac fossa. Adhesions right apex and over left lung posteriorly, to pericardium and to diaphragm. Right lung—thick, puckered pleura at apex with hard, irregular, non-caseated nodule. Small nodules in middle lobe. Left lower lobe nodular. Infarct of spleen. Horseshoe kidneys.

(See Chart, page 203.)

CONDUCT CHART

YEAR	1898	1901	1902
MONTH	AUG.	DEC.	JAN.
NOISY	±		
IRRITABLE	±		
OBSCENE	±		
PROFANE	±		
UNTIDY	±		X
APPETITE POOR	±	X	X
ILL		X	X





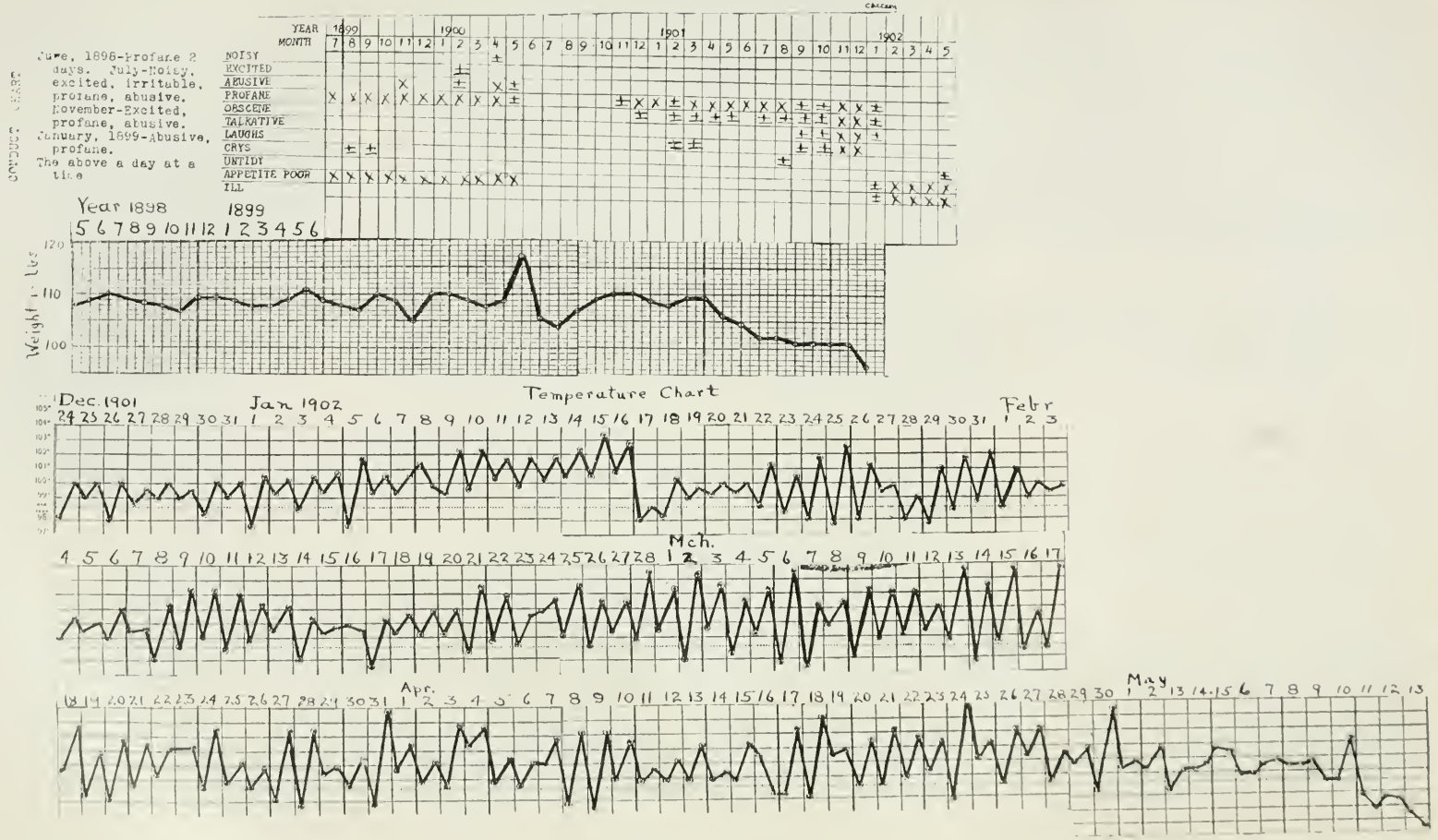
(See Table, page 202.)

CASE VII-46

PHYSICAL	MENTAL	SUMMARY
	1895—Threatens husband and mother-in-law. Profane and vulgar to unseen people. Irritable, laughs and talks to self. Unusual libido et potentia.	Sudden onset at 27 with delusions of a sexual nature and with hyperkinetic signs. One year later, demented. Next three years, periods of activity, gradually losing memory, etc. In sixth year of the disease, signs of pulmonary tuberculosis. Death at 34, one year later.
	1896—Demented.	
	1898—Aggressive, irritable, abusive, profane. Sex delusions about husband and his mother. Works, attends entertainments, does fancy work.	Autopsy—Fluid in abdomen. Right upper lobe anteriorly adherent, externally and posteriorly throughout and to diaphragm. Left adherent externally and posteriorly throughout and to diaphragm. Free fluid in chest.
	1899—Oriented for time and place. Careless appearance. March—Will not work. July—Agreeable and helpful. Aug.-Oct.—Profane.	Right lung, nodular. Bean to hickory-nut size cavities with pus in upper lobe. Gray, white elevated nodules in lower lobe. Left lung nodular; interlobar adhesions. Small, pus cavities in upper lobe and large, empty cavity in lower lobe. Ileum—2 meters above cecum, healed ulcers 2x3 cm., raised, white edges and dark gray bases. Lower is transverse constriction with gray base. Ulcers cecum.
1901, Dec.—Right apex dull front and back. Anemic.	1901—Laughs several months.	
1902, Jan.—Dull first and second space and posteriorly to second spine. Breath sounds harsh. Rales. Large amount of albumin, few epithelial casts. Feb.—Tuberculosis in sputum. Considerable albumin, granular and epithelial casts. Apr.—Spits blood.	1902—Thinks here four years.	

(See Chart, page 205.)

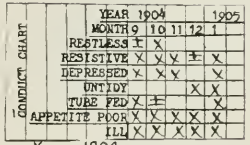
Case VII-46

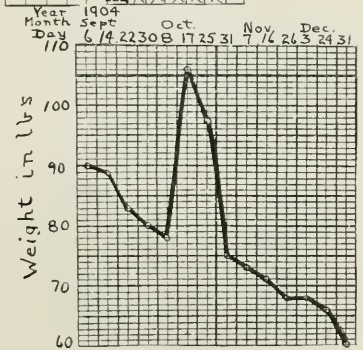


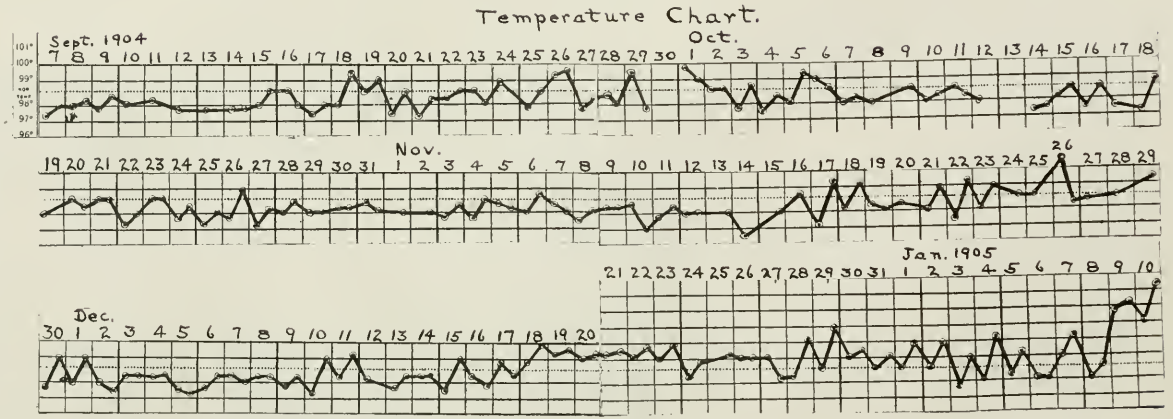
(See Table, page 204.)

CASE X-21

PHYSICAL	MENTAL	SUMMARY
1904, Jan.-Sept.—Headache, loss of appetite and weight, insomnia, feeble. On admission—reflexes brisk. Rare hyaline cast.	1904, Jan.-Sept.—Afraid she is going to die. Mute, confused, hallucinated (auditory). Tried to bite mother. Ran about house till exhausted, then tried to jump from window. Complains of taste of food. Admitted in September, mistakes identities. Resistive, untidy, vermin. Dazed expression. Disoriented. Recent memory poor. Sept. 30—Restless, facial expression stolid, mute. Spoon fed. Oct.—Tube fed. Diarrhea. 1905, Jan.—Untidy. Spoke to nurse and hoped to get well.	Sudden onset at 22 with active physical and mental symptoms. Admitted in dazed condition. Death at 23 in demented condition. Autopsy—Adhesions right lung anteriorly and to diaphragm, left lung upper lobe, posteriorly. Atheroma of aorta. Aortic valves calcified at bases.

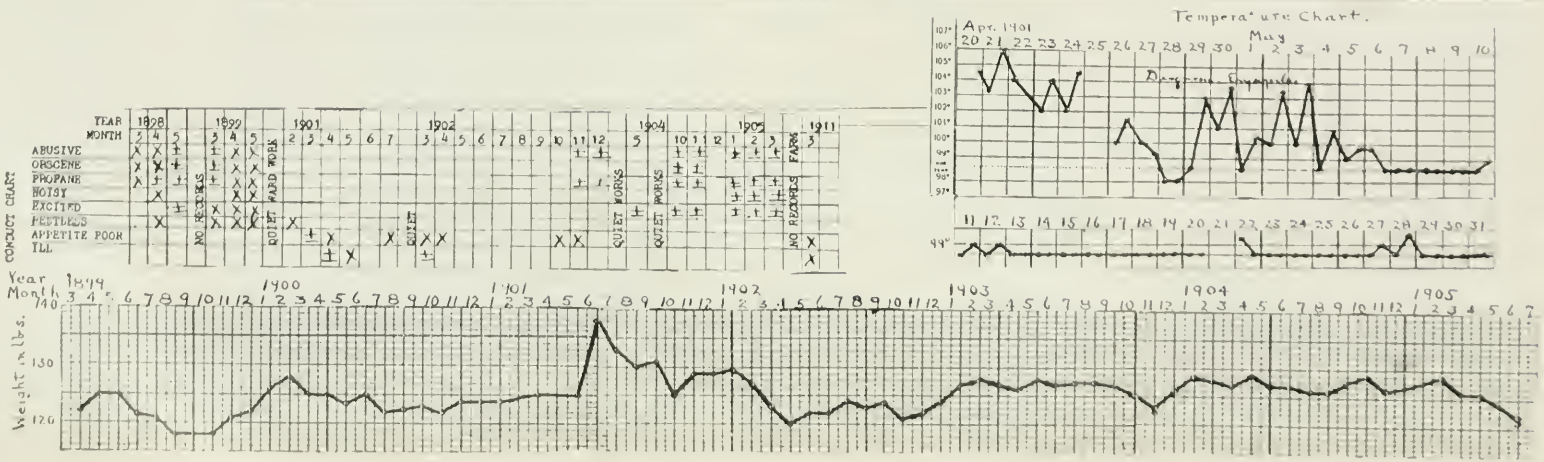






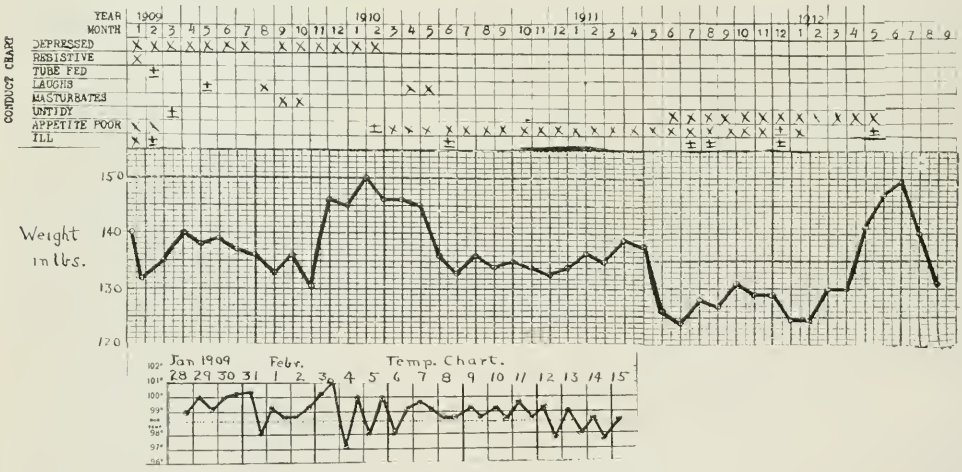
Case XVI-22

PHYSICAL	MENTAL	SUMMARY
Grandmother and brother suicides. 1901—Erysipelas. Diminished breathing right with increased vocal fremitus. "Limbs are stiff." (See temperature chart.) 1905-1911—Worked at farm. March 19—Pneumonia. March 25—Death.	1890—Nervous, ideas of persecution, aggressive, violent. 1891—Irritable, abusive. "His voice is carried everywhere in the building." 1892—Demented. 1894—Abusive, vulgar, irritable, changed his name. 1896—Excited if called by correct name. 1898—Profane, active. 1899—People here have hands, feet, and heads cut off and wear his clothes. 1901—Threatens homicide. Disoriented. No insight. "Building a throne, he is king, patients are all convicts." 1902—Irritable, expansive. 1903—Abusive. Works. 1904—"Silent conversation" (auditory hallucinations). 1905—Disoriented, time and place. No hallucinations. Does not recognize physicians.	Active onset at 29. Admitted at 30. Next 14 years dementia broken by active periods with hallucinations and delusions. Next 6 years dull, mentally inactive, working. Autopsy—Right pleural cavity obliterated, left shows adhesions at apex. Right apex large, irregular, sunken, stellate scar. At base, cordlike mass of encapsulated, yellow, caseous material. Other nodules in relation to cicatrix. Pneumonia and pneumococcus meningitis.



CASE XVII-57

PHYSICAL	MENTAL	SUMMARY
Paternal grandmother insane. 1908—Headache. 1909, Jan.—Tremor of tongue and hands. Urine negative. Feb.—Says he is weak. (See temperature chart.) 1912—Typhoid, positive Widal. Exitus.	1908—Irritable, worried, sat gazing into space. Thought family against him. Said to have chased women and to have exposed himself. Threatened homicide. Confused, seems stupid. 1909, Jan.—Suspicious, laughter explosive, apprehensive, ideas of reference, somatic and sexual ideas, word salad, depressed, resistive. Admitted. Feb.—Hesitant. "Would like to freeze up dead." Tube fed. Oct.—Light work. Reticent. Masturbates and exposes self. Resistive. Whispers under breath. 1911—Silly, grins, repeats questions, dull, disoriented.	Onset at 25 with mild, active symptoms. Admitted less than a year later. Rapid course of three years with catatonic features. Death from typhoid. Autopsy—Adhesions right lung, diaphragm and base. Apical, puckered scars each apex. Ulcers ileum.



There are pleural and peritoneal adhesions and pulmonary emphysema. A tuberculous nodule appears in the kidney.

The thirty cases selected, then, show something more convincing as to the connection between them and tuberculosis than the mere incidence of death from tuberculosis. Seventeen cases, to be described later, or 56.6 per cent show a connection so apparent that they are considered to belong to the toxic-infectious group by some. Thirteen cases considered here show a course which may in a fairly definite way be considered to be bound up with a clinical or anatomic tuberculosis. Tuberculosis was demonstrated anatomically in all of them and the anatomic picture was the one to be expected from the course of the mental picture, the physical signs, such as weight and the subjective symptoms, and from the temperature chart.

SUMMARY

There is a definite group of cases of dementia precox in which tuberculosis may be considered to be a causative factor and, possibly, the causative factor.

Of such a group, 73.3 per cent die of tuberculosis. In 56.6 per cent the courses of the mental and the physical disease run parallel and in the other 43.3 per cent, which is the percentage which recover and die of a later tuberculosis or of some other cause, a previous or concurrent tuberculosis is demonstrable.

Special complement-fixation tests on the blood and spinal fluid and special cultural methods applied to such cases should yield a high percentage of positive results and give us an added advantage in early diagnosis.

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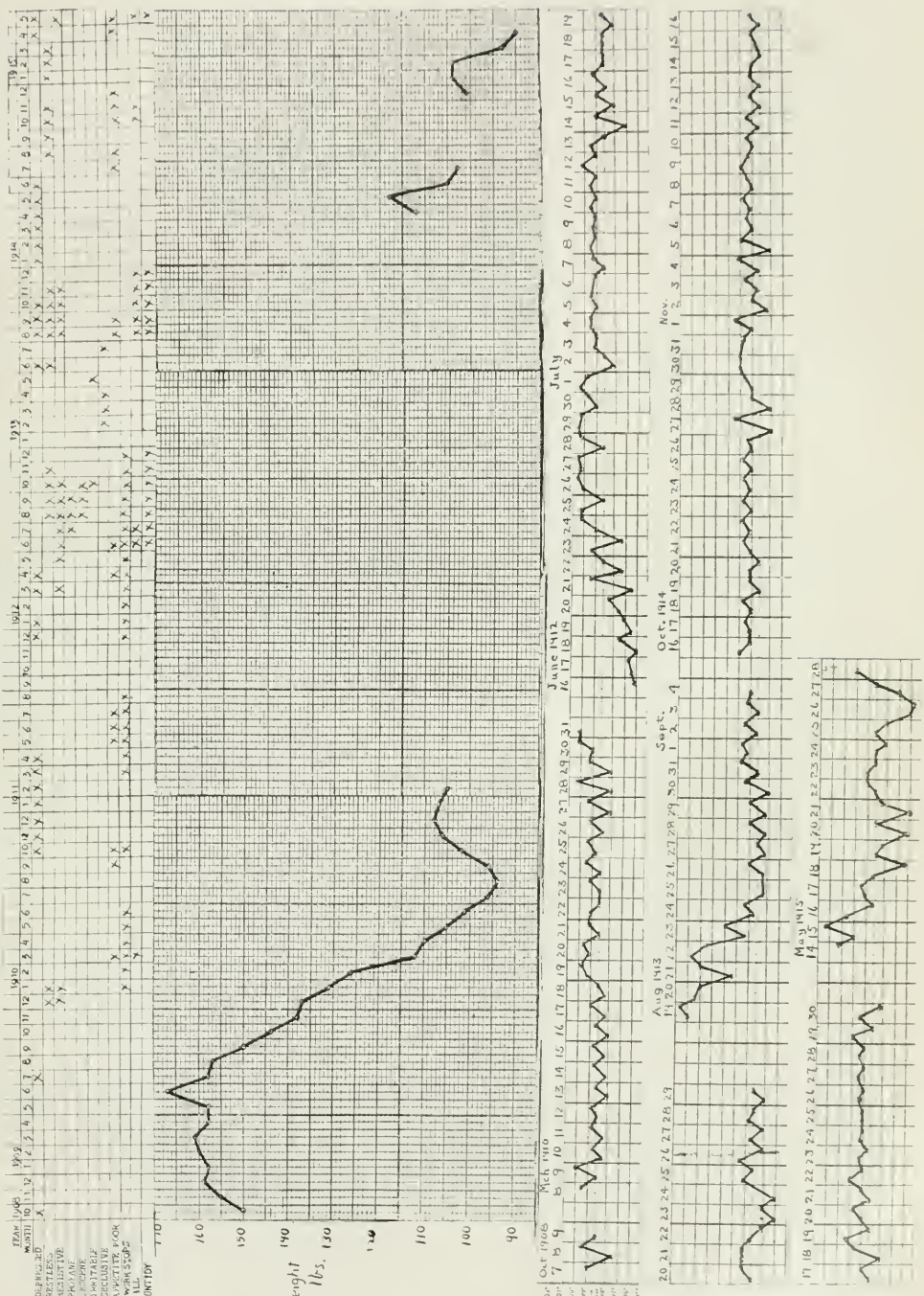
[4]Bronfenbrenner, J., Kahn, Morris, H., Rockman, J., Kahn, Max: Further Studies of Biological Methods for the Diagnosis of Tuberculosis, Arch. Int. Med., 1916, xvii, p. 492.

CASE 1915.18

PHYSICAL	MENTAL	SUMMARY
	1902—Ideas of reference, auditory hallucinations, ideas of persecution. Went to the roof to escape voices. Depressed. No insight.	Onset gradual and with remissions at 44 (?). Symptoms improve with hospital residence, grow worse outside and with gradual dementia of moderate degree. Weakness from beginning. Finally signs of pulmonary trouble.
1903—Had a "numbness in her fingers." Reflexes exaggerated. Appetite poor.	1903—Admitted to McLean Hospital—depressed and hallucinated at times. Released but later returned. "Priest made faces at her," voices dictated orders which she obeyed. Suspicious and seclusive. Incoherent. Transferred to Worcester.	Autopsy—Adhesions right upper lobe, posteriorly; both lungs to diaphragm. Fluid, left chest. Right lung, cavity at apex, tubercles in lower lobe. Left lung, surface nodules in upper lobe, coalescing tubercles forming abscess cavities in lower lobe and subpleural hemorrhage.
1904—Has stomach trouble and feels tired, calls it dyspepsia.	1904—Discharged. Went to church every day, troubled by "martial law."	Irregular, circular ulcers ileum near cecum.
1908—Is very tired. Appetite good. Sleeps well. Hair dyed.	1908—Returned. Excited. "Went to church to get rid of treason." Laughs and mumbles. Memory good. Oriented. "Voices defame her character." Reticent. No insight.	
	1909—Seclusive, intractable at times.	
1911—Albumin present, hyaline, waxy, granular casts, edema of ankles, diarrhea.	1911—Memory impaired, reticent, ideas of reference and persecution.	
1913—Dysentery. Trace albumin, few red cells.	1914—Unoccupied, seldom speaks, dull. Disoriented, memory poor, deluded.	
1914—Feet bother her. She is tired. Albumin, s. p. t. Emaciated. Sounds rough at apices. Wassermann, blood, negative. October — "dysentery."		
1915—Cough, sputum negative. Sounds harsh, rales. Red cells, 4,216,000. White cells, 35,440. Hb. 75%. Exitus.	1915—Apathetic.	

(See Chart, page 211.)

CASE 1915.18



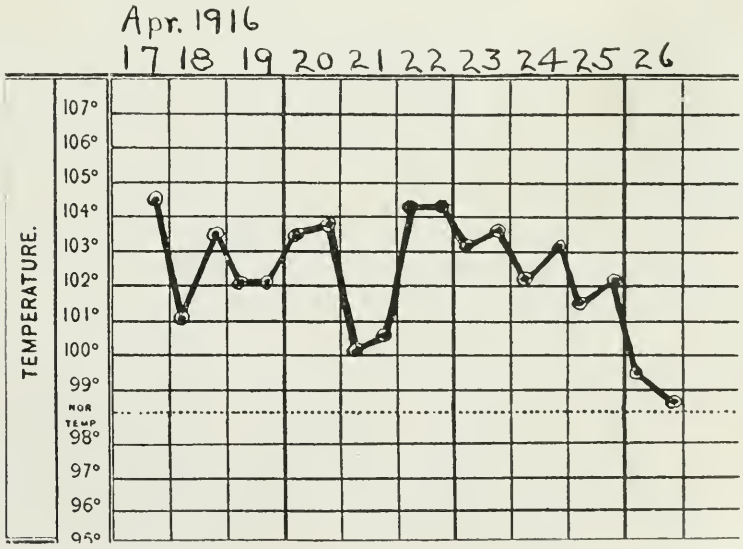
(See Table, page 210.)

CASE 1915.25

PHYSICAL	MENTAL	SUMMARY
One sister died of tuberculosis. Complains of headaches many years. 1914—Tremor hands, gait unsteady. Albumin, slight trace. Wassermann on blood negative. 1915, Feb.—Muscular resistance. Impaired resonance, sounds diminished, left side. Appetite ravenous. July—Contractures. Death.	Many years has frequently repeated phrases. 1913—Has developed mannerisms and delusions. 1914—Violent. Auditory and visual hallucinations. Mute, resistive, at times active and destructive. Admitted—Untidy, resistive, replied by gestures and mannerisms. Later, restless, demudative, irritable, abusive, profane. Attention poor, irrelevant, disoriented, mistakes identities, memory impaired. Nov.—Spoon fed, then tube fed, negativistic, mute. 1915, Feb.—Mutters and verbigerates, incoherent. May—Restless, noisy, untidy.	Peculiar actions together with headaches for years. At 48 active mental and physical signs which continue till death one year later. Autopsy—Left pleural cavity obliterated. Small area of pneumonia in right upper lobe (probably tuberculous). Lungs fibrous throughout.

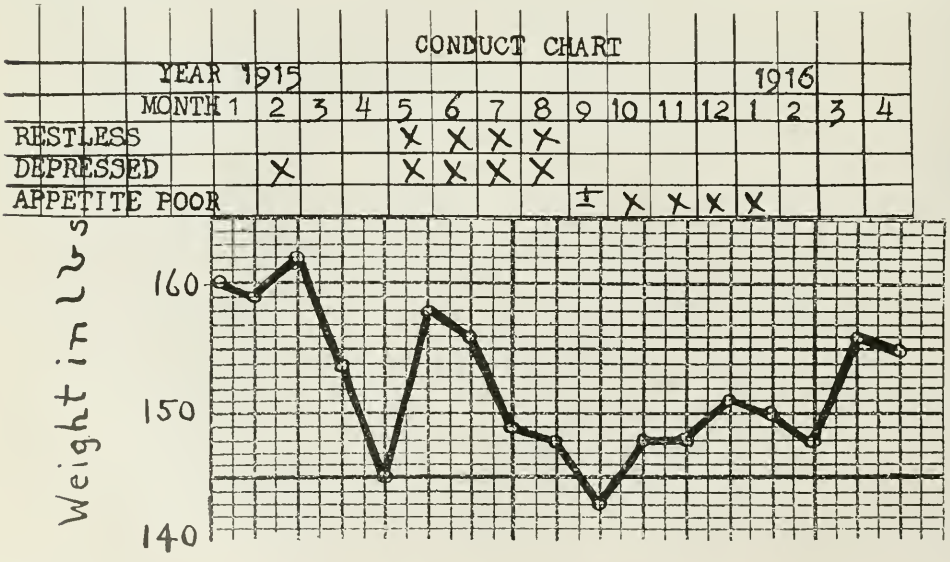
CASE 1916.36

PHYSICAL	MENTAL	SUMMARY
	1887—Moody, sensitive, unreasonable.	At 25 gradual onset with character change. Two years later dangerous. Four years later, hallucinated, homicidal. One to four years later, deluded, incoherent, profane. Seven years later indifferent to hallucinations. Nine years later, ideas of reference, irrelevant.
	1889—Dangerous. Hospital, August to November and discharged.	
	1893—Attempted homicide. Hears name coupled with false and vile statements.	
	1894—"Twenty men murdered every night on the ward." Incoherent. Works.	
	1898—Talks to self but not so profane as formerly.	
1902—Weight, 138 to 145 pounds.	1905—Indifferent, oriented, "voices sound like telephone," profane.	
	1906—Talkative, profane, fair grasp on current events.	
	1914—Hallucinated but "not bothered by them."	
	1915—Irrelevant at times. "People look at him in a peculiar manner and read his thoughts."	
1916—Returned from farm, pneumonia. Weight 121 pounds. Death.		



CASE 1916.37

PHYSICAL	MENTAL	SUMMARY
1910—Easily tired. Nausea, dizzy, weak, dyspneic. Urine negative. 1914—Dysentery. Urine negative. Heart slow, pulse 30 per minute. 1915—Wassermann on blood, negative. 1916, April—Died.	1879—Onset. Untidy, lazy. Masturbates. "Head empty, brains soft." 1882—In Tewksbury. Transferred to Worcester. 1883—Deluded. Tries to burn hair on gas jet. 1886—Talks to self. 1888—Has to be coaxed, irritable. 1905—Has worked at Farm till now. Memory good. Says his delusions were imaginary. Previous visual hallucinations. Claims he got his head jammed between a building and a sleigh. 1910—Works at farm or hospital. Dull. 1912—Apathetic, oriented. Admits previous hallucinations and delusions. 1913—"Picture of depression."	Onset at 28 with mild mental and physical symptoms. Admitted at 31 in dilapidated condition. Improves but remains demented. At 59, signs of vascular trouble. Autopsy—Adhesions of cecum to lateral abdominal wall and of right and left lower lobes to pericardium. Emphysema. Small, white nodule, surface of right kidney. Granular growth from dura separating convolutions in region superior parietal.



LABORATORY METHODS

A MODIFIED HECHT-GRADWOHL TEST FOR THE SERUM DIAGNOSIS OF SYPHILIS*

By W. J. Bruce, New Rochelle, N. Y.

IN reviewing the literature, one is certainly impressed with the many different methods of performing the complement fixation. For years serologists have been trying to devise a satisfactory method of controlling two important factors in this reaction, namely, native complement and native antisheep amboceptor.

Heating serum at 56° C. for 30 minutes destroys the natural complement, but this is a disadvantage, as suggested by Vladimir Busila's[1] work in 1910. He found that sera have two syphilitic antibodies, the one is thermolabile, or destroyed when exposed to a temperature of 56° C., the other thermostable, or unaffected by this degree of heat. These are present in both blood and spinal fluid in varying proportions, and the thermolabile is the first to appear in the blood and the last to disappear under treatment. He also found that when the thermolabile amboceptor is present alone, the Wassermann with heated serum will give a negative result, while with unheated serum a positive result. As the thermolabile antibody often exists alone in nervous, latent, and insufficiently treated syphilis, using the Wassermann technic of performing the test with inactivated serum results in a considerable error in these cases. Noguchi[2] has shown that syphilitic serum heated at 55° C. for 30 minutes loses about one-fourth to one-fifth of its syphilitic antibody.

There are several methods which use the complement in fresh human serum with a fixed amount of amboceptor, but as the native complement is so variable these methods are unreliable unless the serum is titrated for the exact amount of complement present.

Natural antisheep amboceptor is unaffected by heating at 56° C. over a reasonable period, although the complement is eliminated at this temperature. By the addition of sheep red blood corpuscles to inactivated human serum, the native antisheep amboceptor will be absorbed, but this is a tedious procedure, and is seldom carried out routinely. To prevent this native amboceptor entering the test at all, Noguchi[2] used an antihuman, Browning and Mackenzie an antiox, and some workers even produced an antichicken amboceptor.

Hecht and Weinberg[3] in 1909 published a method using the fresh noninactivated human serum and utilizing the native alexin or complement and native antisheep amboceptor. Their method is conducted as follows: Four tubes are used in the test, each tube receiving 0.02 c.c. of fresh patient's serum.

*Read before the St. Anthony's Hospital Clinical Society, Oklahoma City, May 20, 1918.

The antigen used is an alcoholic extract of human heart. Tube No. 1 receives 0.08 c.c. of a 1-50 dilution of antigen, and tube No. 2 receives 0.08 c.c. of a 1-100 dilution, and tube No. 3 receives 0.08 c.c. of a 1-200 dilution, while tube No. 4, which is the serum control does not receive any antigen, but 0.08 c.c. of normal saline. The tubes are placed in the water-bath for ten minutes, and 1 c.c. of a 1 per cent suspension of sheep cells is added to each of the four tubes, and these are reincubated for ten minutes, when the control must show hemolysis; but if it does not, the test is worthless on that particular serum. If a strongly positive acting serum is present there will be complete fixation in all three tubes containing antigen, the control tube showing complete hemolysis. In case the serum is a weakly positive acting one, there will only be complete fixation in the first tube containing the 1-50 dilution of antigen, with the remaining tubes showing hemolysis. A negative serum gives complete hemolysis in all four tubes.

This test is very simple, but unreliable, as it titrates the patient's serum for syphilitic antibody, but not for native complement and amboceptor. The use of such a large arbitrary dose of sheep cells in the presence of such a small amount of serum, leaves this test applicable only to sera of high hemolytic titer. When the control tube does not show any hemolysis, one of two things is at fault, either the patient's serum is low in native hemolysins or an overdose of sheep cells has been added.

Gradwohl[4] saw the possibility of using this test on almost every human serum, as it is estimated that 98 per cent of Americans have some antisheep amboceptor present in sufficient quantities to be utilized. He therefore modified the method of Hecht in such a manner that when the principal test is made it is impossible to have a lack of hemolysis in the serum control tube. A preliminary titration for the exact amount of native hemolysins is first made. His technic is as follows: Place in a rack fourteen small test tubes. The first ten tubes are used to determine the "hemolytic index" of the suspected blood. The last four tubes are used in the actual test. To each of the first ten tubes are added 0.1 c.c. of fresh, unheated patient's serum, then decreasing amounts of normal saline are added to each of these tubes, beginning with 1 c.c. and ending with 0.1 c.c. Next increasing amounts of a fresh 5 per cent suspension of sheep's blood are added, starting with 0.1 c.c. and ending with 1 c.c. Now the rack is placed in the water-bath for thirty minutes. The last tube which shows complete hemolysis constitutes the "hemolytic index" of that serum. If it is tube No. 4 the index is four, because this tube had received 0.4 c.c. of the sheep cell suspension, so therefore, we have obtained an idea as to how much of this suspension is to be added to the last four tubes. The first three tubes, (11, 12, 13) constitute the tubes for the actual test, while the last tube in the rack, (14) serves as the serum control tube. Tubes 11, 12, and 13, receive therefore, the patients' serum, the proper amount of sheep corpuscles (depending on the "hemolytic index"), increasing strengths of antigen, but no complement and no amboceptor. Tube No. 14 receives only patient's serum and sheep corpuscles, but no antigen. One-tenth c.c. of a dilute antigen determined by titration is used in tube No. 11, 0.15 c.c. of antigen in tube No. 12, and 0.2 c.c. in tube No. 13. All the tubes are equalized with normal saline so that each tube contains 0.4 c.c.

of solution. The tubes are agitated and placed in the water for thirty minutes.

The last four tubes are filled at the time of making the additions to the first ten, and are left with them in the water-bath for a half hour for the fixation of the complement. The rack is then taken out and the "hemolytic index" computed. If the index is low, say from 1 to 4, 0.1 c.c. of the sheep cell suspension is added to the last four tubes; if between 5 and 7, 0.15 c.c. is added; and if 8 to 10, 0.3 c.c. is added. But if the index is over 10, the titration for the amount of natural hemolysis is repeated, and if the index falls between 11 and 15, 0.25 c.c. is used, if between 15 and 18, 0.3 c.c. is used, and if between 18 and 20, 0.35 c.c. is used. If a serum has an index below 2, the reaction is regarded as of doubtful value, but if above 2, it is of absolute value. The reaction is read as in the Wassermann, that is, inhibition or noninhibition of hemolysis. If the amount of natural complement or natural antisheep amboceptor is very low, guinea pig serum or immunized rabbit serum can be added in proper proportion ascertained by a preliminary titration. There is no technic given of the method of titrating the antigens for this test.

In a series of 360 persons, Kolmer[5] subjected the sera of each case to both the Wassermann reaction and the Hecht-Gradwohl test, with the same antigens used in each method. His technic is slightly different from that of Gradwohl, as he used fewer tubes for determining the hemolytic index, and instead of adding a certain quantity of sheep cells, according to the sliding scale of Gradwohl, he used one-half the "hemolytic index." The incubation period is also extended from thirty minutes to one hour. The serum is not titrated for syphilitic antibody, and the dose of antigen is 0.2 c.c., and equal to 4 or 5 antigenic units. With this method the same results were obtained in 82 per cent of these cases, 40 per cent were positive in both, 60 per cent were negative with both methods, 12 per cent more positive results were obtained with the Hecht-Gradwohl than with the Wassermann test.

In this laboratory a Wassermann and a Hecht-Gradwohl control is made on every specimen of serum, provided there is a sufficient quantity of serum, and native hemolysins. The routine followed is so arranged that the control test will not interfere with the work of setting up the Wassermann test. A sufficient sheep cell suspension is made to allow 8 c.c. for each specimen to be tested. The human serum is freed of red blood cells, and a certain amount is placed in a rack for inactivation, and the remaining serum is placed in another rack for the Hecht control test. The antigen is now diluted to the proper strength.

The titrations of guinea pig serum and amboceptor for the Wassermann test is next made and placed in the water-bath, and the racks of patient's sera that have already been prepared are placed in a water-bath to inactivate. Work can now be commenced on the Hecht-Gradwohl test, and usually this test is ready to be incubated before either the hemolytic titrations, or the Wassermann sera are ready to be taken out. During this time the sera are prepared, and the titrations for the Wassermann are being made, the Hecht-Gradwohl test is in the water-bath, allowing work on the Wassermann test to commence immediately, and with no loss of time.

The following technic has given the best results in our hands. The specimen is collected within 48 hours of performing the test. About 8 or 10 c.c. of blood is drawn into a sterile container and allowed to clot at room temperature. The clot is now separated from the test tube and the specimen placed in the refrigerator overnight. The following morning the tube is centrifuged and the clear serum pipetted off into a sterile test tube, and again placed in the refrigerator until the test is made. Sera treated this way have shown a fairly high "hemolytic index" after 72 hours. Although 8 per cent of our sera failed to give any hemolysis, many of these were collected and sent to the laboratory by mail, and therefore, did not receive the proper attention to prevent the deterioration of the native complement. No attempt was made to add any amboceptor, or replace the complement in these seras.

SHEEP CELL SUSPENSION

Fresh sheep blood is used. This is washed with normal saline until the supernatant fluid is albumin negative with the heat and acetic acid test. A 3 per cent suspension of washed cells is made in sufficient quantity to complete the test on all the sera. As each test requires about 8 c.c. of this suspension, 100 c.c. will be sufficient for 12 different sera. The cell suspension used to titrate for the hemolytic index must be used in the final test.

ANTIGEN

Organic extracts are capable of hemolyzing red blood cells due to hemotoxic action of alcohol and lipoids. For this reason the antigen must be titrated for its hemolytic unit. Ten test tubes are placed in a rack and the following amounts of a 1-10 dilution of antigen are added, i. e., 0.2, 0.4, 0.6, 1.0, 1.2, 1.5, 2.0, 2.5, 3.0 c.c. Each tube now receives 0.5 c.c. of 3 per cent cell suspension, and the volume brought up to 3.5 c.c. with normal saline. These are incubated for one hour at 38°C. and the first tube that shows the slightest hemolysis is considered the hemolytic unit.

ANTICOMPLEMENTARY TITRATIONS

Serum is obtained from three healthy nonsyphilitic Wassermann negative persons. These sera are pooled and titrated for the hemolytic index.

Twelve test tubes are racked up and each tube receives 0.1 c.c. of this pooled serum with varying amounts of a 1-10 dilution of antigen ranging from 0.1 c.c. to 2.0 c.c. A tube containing serum but no antigen is used as a serum control. All the tubes are brought up to a volume of 2.5 c.c. (less one-half the hemolytic index) with normal saline, and incubated in the water-bath for one hour. One-half the known hemolytic index is then added and reincubated for another hour. The first tube that shows the slightest inhibition of hemolysis is recorded as the anticomplementary unit. The serum control tube must show complete hemolysis.

ANTIGENIC TITRATIONS

Pooled serum from three syphilitic Wassermann positive patients is used. The hemolytic index is determined, and 0.1 c.c. of this serum is added to twenty

test tubes. Each tube receives varying amounts of a 1-10 dilution of antigen ranging from 0.01 c.c. to 0.2 c.c. The hundredths of antigen were diluted so that 0.1 c.c. equaled 0.01 c.c. of a 1-10 dilution. A serum control is also used. The remainder of the test is conducted as for the anticomplementary unit. After the tubes are reincubated they are placed in the refrigerator overnight, and the first tube showing complete inhibition of hemolysis is considered the antigenic unit. The antigen used in our work was the protein free, reprecipitated, acetone insoluble lipoids, prepared according to Noguchi. Four or five antigenic units was the dose used in the principal test, and this amount was less than one-twentieth the anticomplementary unit.

TECHNIC OF THE TEST

Twelve tubes are placed in a rack and all these receive 0.1 c.c. of the suspected noninactivated serum. To the first ten tubes varying amounts of a 3 per cent suspension of washed sheep cells are added, beginning with 0.2 c.c. and ending with 1.1 c.c. Normal saline is now added to bring the volume of these ten tubes up to 2.0 c.c. Tube No. 11 is the antigen tube, and receives the proper dose of antigen, as determined by titration, while tube No. 12 is the serum control and does not receive any antigen. Sufficient normal saline is added to these two tubes to make a volume of 0.5 c.c. The racks are placed in the water-bath for one hour at 38°C. and shaken occasionally. At the end of this time the racks are removed and the last tube which shows complete hemolysis is considered the hemolytic index. At this point the first ten tubes are discarded, and one-half of the hemolytic index is added to each of the two remaining tubes. These tubes are thoroughly shaken and reincubated in the water-bath for another hour, and placed in the refrigerator overnight.

When a negative result is obtained, hemolysis usually occurs within the first ten or fifteen minutes, and if a positive reaction is present, we have a picture similar to a four-plus positive Wassermann. Only in cases that are Wassermann negative, and are receiving thorough treatment, do we get a tube showing partial hemolysis. It is important that all the tubes be thoroughly shaken every ten or fifteen minutes during incubation.

Sellards and Minot[6] published, in 1916, a series of 134 cases, in which they found only 14 sera, containing two or more units of natural antisheep amboceptor, and were unable to offer an explanation for the lack of hemolysis.

If these workers used fresh active serums, their trouble was undoubtedly due to a too heavy sheep cell suspension. Gradwohl has constantly obtained a positive Hecht-Gradwohl when the Wassermann was positive, and 15 per cent more positives than with the Wassermann reaction. Kolmer's figures are 18 per cent more true positive results with an acetone antigen than with the Wassermann test. If the blood was collected within 48 hours of making the test, he found there was sufficient native complement and native antisheep amboceptor present to conduct the test. In our series of 608 sera 8 per cent failed to hemolyze any sheep corpuscles. The Wassermann test performed with active and inactivated sera and the Hecht-Gradwohl, with the modification given above

was paralleled on 532 sera. Positive Wassermann with positive Hecht-Gradwohl tests were obtained on 105 or 20.6 per cent; negative Wassermann and negative Hecht-Gradwohl tests were obtained on 395 sera or 74.2 per cent. Positive Hecht-Gradwohl tests and negative Wassermann tests were obtained on 32 or 5.7 per cent of these cases.

While these figures are considerably lower than either those of Gradwohl or Kolmer, yet this difference can probably be explained by the method used in the Wassermann test. In our Wassermann technic we use both inactivated and noninactivated serum and even if there is an absence of fixation with heated serum, and present with unheated serum the test is reported as positive. If you compare our results with a Wassermann, made with heated serum alone, our results would correspond with those of the former writers.

CONCLUSIONS

In primary syphilis the modified Hecht has always shown up positive in from one to two weeks earlier than the Wassermann. A positive result can usually be obtained in from one to two weeks after the initial lesion with this test. In treated cases the Hecht-Gradwohl has always been the last to disappear. This test has its greatest value as a serological control in the treatment of syphilis, and in the interpretation of a weakly positive or "borderline" Wassermann reaction. It must be conducted with a properly standardized antigen, the proper dose of sheep cells, and fresh noninactivated sera. With the technic just described we have not found a single case in which the Wassermann was positive and the Hecht-Gradwohl negative. Although this test is more delicate than the Wassermann reaction in the serological diagnosis of syphilis, yet it can not be utilized on every serum due to the lack of native hemolysins, and must therefore serve the purpose of a control test.

The observations of Sellards and Minot have not been confirmed.

I am deeply indebted to Dr. O. J. Walker for his many suggestions and able assistance in the preparation of this paper.

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A SIMPLE DISTILLING APPARATUS*

By A. L. Garbat, M.D. (New York City)
Captain, M. C., U. S. Army; Chief of Laboratory, General Hospital No. 12, Biltmore, N. C.

A SIMPLE, inexpensive and rapid device for obtaining distilled water has been devised. The only essential is steam pressure.

The main pipe conveying the live steam to the laboratory runs along the wall about six feet from the floor. A three-quarter inch pipe (A) is led vertically downward from the main pipe to several inches from the bottom of the sink basin and then continued transversely for about nine inches where it opens into the basin. At about six inches from the angle, a "T" connection

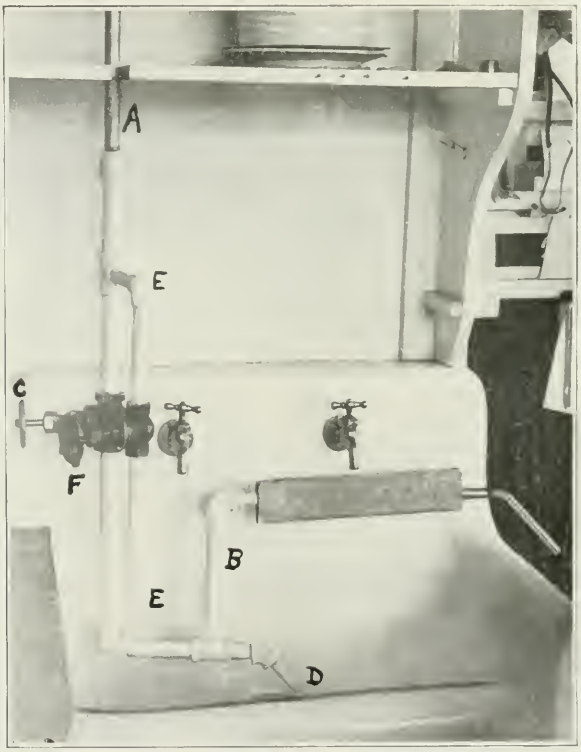

Fig. 1.

is inserted and a half inch pipe (B) extended upward for about nine inches more or less depending upon the height of the water faucet. To the end of this pipe is attached an "L" connection to which the distilling apparatus is screwed when its use is desired, at other times it is disconnected. This vertical nine-inch pipe is bent either slightly forward or backward so that when the distilling tube is attached, it is in line with the cold water faucet (Fig. 1).

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The distilling apparatus (Fig. 2) consists of an ordinary nickel plated or copper tube about sixteen inches long to which is soldered a cradle made of 24 gauge metallic sheet iron. When distilled water is wanted, a valve (C) (Fig. 1) attached to the extension pipe is opened so that a heavy flow of steam escapes from the distilling tube. The cold water is then allowed to run and kept overflowing the cradle; the water within the cradle is constantly cool. The steam at once condenses and distilled water is obtained. By means of a rubber stopper, a bent glass tube may be inserted into the outer end of the distilling tube for carrying the distilled water to a retainer.

A gallon of water is obtained in about forty minutes. A moderate quantity of steam escapes from the lower opening of the pipe (D) into the sink. This can be obviated by placing a moist towel over this exit. The distilling apparatus was purposely not led off directly from the main pipe extending down-

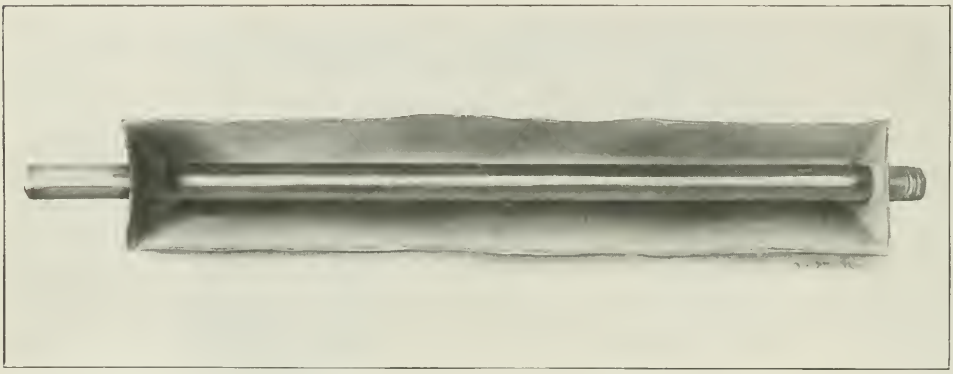

Fig. 2.

ward, so that if any water is condensed on the way from the engine house, it may escape into the sink from the lower exit and only steam will flow upward through the "T" extension. The additional outlet (E) seen in Fig. 1 coming off from the main vertical extension, has nothing to do with the distilling device. It is simply a steam outlet for purposes of disinfection. This extension has its separate valve (F).

For those accustomed to obtain distilled water by means of the ordinary house still, heated by a Khotal burner, this appliance will undoubtedly be of aid. Even the Stokes Automatic Still does not give as much water per hour as does this simple device. It is especially appreciated by those who are so insistent upon the use of absolutely freshly distilled water for Arsphenamine administration.

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Influenza and Pneumonia at Brest, France

FROM April 1 to July 31, 1918, a mild epidemic of influenza and pneumonia prevailed at Brest and in that vicinity. During this time there were admitted to our Naval Base Hospital at Brest, 50 cases of influenza, 26 of whom developed pneumonia, with two deaths. During the same period the French military, civil and naval authorities reported 4,838 cases of influenza, with 688 hospital admissions and 53 deaths. In one station among 1,018 young French recruits, 688 were admitted to the hospital and 49 deaths occurred. The mildness of this outbreak was in sharp contrast to what occurred later. About August 22 a more violent outbreak occurred, and from this date to September 15 there were 1,350 hospital admissions with 370 deaths. However, influenza reached its greatest violence in September, and the pneumonia followed in October. During these months 458 cases of influenza were admitted to our Naval Hospital, with 171 developing pneumonia and 65 deaths. This means a case fatality of 38 per cent for pneumonia. The death rate among cases of pneumonia originating on shore at Brest was 38 per cent, while among those taken from transports it was 48 per cent.

The influenza was characterized by a sudden onset, marked prostration, rapid rise of temperature to 103° to 105°, headache and myalgia, and in severe cases a cloudy skin. The leucocyte count was low, while that of the lymphocytes was relatively high. Throat symptoms were not marked notwithstanding the

fact that in the region of Brest, primary colds are commonly marked by early pharyngitis and even by laryngitis, and sometimes by tracheitis. Epistaxis was frequent. But few cases escaped bronchitis, which appeared in many instances after the temperature had dropped to normal and patients were apparently convalescing. Two cases of influenza showed symptoms strongly suggestive of appendicitis. In only one case was there a definite gastrointestinal form of grippe, showing marked nausea, vomiting, high temperature and severe diarrhea. This patient, after his temperature had reached normal and his diarrhea disappeared, was suddenly seized with severe pain in his right side. His temperature rose to 105°, the leucocyte count which was only 5,000 during his early attack rose to 14,200, and distinct signs of involvement of the right lower lobe appeared. This case finally ended in recovery.

In a large percentage of the cases pneumonia was at first distinctly lobular, but the areas of involvement soon became multiple and of wide extent. Bacteriological study demonstrated the presence of pneumococci, Type I, both in the sputum during life and in the heart blood after death. Many cases were characterized by the usual bloody sputum and some showed a decided increase in leucocytes, though few reached the large numbers usually found in pneumococcus pneumonias. Most cases showed a bronchitis present on both sides and accompanied by cyanosis and extreme dyspnea.

The sputum varied from plain mucopurulent to typical pneumococcic. The influenza bacillus was found in one of the specimens only. In another there was found a pure culture of staphylococcus. These findings were confirmed by securing pure cultures directly from the lungs postmortem. The conclusion was that the disease was a real pneumococcus infection complicated, however, in some instances, with bronchitis in an exaggerated form. In one case hemolytic streptococci were found in the blood during life, and on postmortem examination pure cultures of this organism were obtained from the heart blood in seven cases. Throat cultures made upon admission showed no hemolytic streptococci. In the French hospital at Brest during the same period, of 64 blood cultures, 47 were negative and 11 gave such a varied growth as to suggest contamination. In 6 cases, all severely ill, streptococci were found; in 2 this organism was associated with a diplococcus. Six lung punctures gave pure cultures of streptococci in 4 instances, while 2 were sterile. At the French hospitals the sputum showed streptococcus infrequently, but these organisms were recovered in all cases coming to autopsy, and cultures from the heart blood of those dead of influenza contained streptococci in all instances. In one case where the autopsy was delayed streptococci were associated with a septic vibrio. French observers said that this streptococcus presents the biologic properties of streptococci in general, only occasionally were they of the hemolytic type, and they lay stress on the fact that it is highly virulent for man. This was demonstrated accidentally when one of the French surgeons, who was infected in making a pleurotomy on a case of grippe, died of streptococcus septicemia.

Sixty-nine autopsies were performed at the United States Naval Base Hospital No. 5 on bodies dead of influenza during the last two months. The pathologist thinks that the cases studied here fall among the lobar type rather than

under the massive bronchopneumonia type. From clinical experience alone one would have expected to have a larger number of bronchopneumonias, but recoveries among this type of cases were perhaps proportionately larger.

Masks appeared to be of value in limiting the transmission of influenza from patient to patient as well as from patient to nurse and to hospital corpsmen. Masks are not recommended for pneumonia patients, as they interfere with the breathing and are rarely kept in place. The beds in the hospitals were converted into cubicles, and it is believed that this procedure was of service.

The conclusion of this report, which is made by Lieutenant Commander James E. Talley, M. C., U. S. N. R. F., is stated as follows:

"A very severe epidemic of influenza has just ended in which over 10 per cent of the cases appearing at this station developed pneumonia which clinically usually developed as a lobular pneumonia but tended to involve wide areas. Influenza bacilli were demonstrated but rarely. This we believe has been a common experience in France. However, the possibility that a filterable virus is the cause of influenza is not yet excluded, and one is just beginning to hear more of the filterable coccoid form of the influenza bacillus. There seems good reason to believe that streptococci and various pneumococci are often secondary invaders, because in the same epidemic the same workers in different places have found different bacteria predominating. For instance, one hears that Dr. Martin, the subdirector of the Pasteur Institute, who spent some weeks here when streptococci seemed to be most active, now finds pneumococci the commonest bacteria in his material, whereas in other parts of Paris streptococci still predominate. Here in the local French hospitals, where earlier one found only streptococci, many pneumococci are now seen."

—*V. C. V.*

Influenza in Camp Custer

THIS report was made by Major John S. Billings. The epidemic made its appearance at Camp Custer on September 23. It followed an increased prevalence of coughs, colds, tonsillitis, bronchitis, pharyngitis, etc. The total strength of the command is that of October 1, 1918, and is given as 39,678. It is a question whether the colds, etc., referred to as having occurred before September 23 were or were not cases of influenza. At least on and after September 23 these cases were diagnosed as influenza. From September 23 the number of cases increased in fairly regular geometrical proportions, reaching its maximum on October 2 when 1,227 cases were admitted. The crest of the wave held for about four days, when a fall followed. The regression was steady and continuous, the number falling below 100 on October 14, below 50 on October 20, below 20 on October 24, and below 10 on October 29. The epidemic was declared closed on November 3.

The epidemic appeared in the 78th Infantry first, which numbered 3,561. The general sanitary condition of this command was excellent in all respects save one. All organizations were instructed to boil their mess kits, the order

being issued in August, 1918. Through some confusion and delay the 78th Infantry did not begin sterilizing their mess kits until September 26.

The 160th Depot Brigade numbered 14,048, making more than one-third of the entire command. The units of this brigade were widely scattered throughout the camp and under varying housing conditions. Their make-up also differed—some consisting of negro troops, others consisting largely of venereal cases.

The 41st Field Artillery had the greatest number of cases in proportion to its strength (543 per 1,000). Major Billings says that this may have been due to one of two things: (a) on October 5 a detail of 100 men from this organization was sent to the Base Hospital Annex for night work, returning to their barracks the next day. On October 6 a new detail of 100 men did the same thing, and 35 on October 7. The morbidity increased from 14 cases on October 5 to 135 on October 6; (b) this organization had among its sick the highest proportion of men of less than two months in the service.

Field Artillery No. 42 came next with a morbidity of 509 per 1,000. No reason could be found as the regiment was located in a very desirable part of the camp. Its percentage of new men was low and special precautions were taken to quickly isolate new cases. No man with a temperature over 100° was detailed to fatigue duty. The 10th Infantry had the lowest morbidity (162 per 1,000) with 30 per cent of new men. Next in order came the Sanitary Train with 163 per 1,000, and 57 per cent of new men.

Of the total of 10,421 cases, 4,668 were admitted direct to the Base Hospital, 5,457 to the particular Regimental Hospital, and 296 were sent to quarters.

It was the opinion of the organization surgeons that typical cases of influenza were seen as early as September 22, and while the severity of the cases became greatly intensified, the change was one of degree only. However, at the Base Hospital it was felt that few cases of true influenza were admitted prior to September 27. The entire symptom-complex seemed to change on that day, and the cases admitted to the hospital from then on were of a very different and more severe type. The earlier cases were recorded as simple bronchitis and pharyngitis of no great severity, the majority soon recovering. The epidemiologist says that he can give no information as to which group of observers was correct, but consideration of the records would make it seem unlikely that there were two distinct diseases for the following reasons:

1. No cases of simple bronchitis or pharyngitis were reported after September 29, although on the four preceding days there were 577 cases of bronchitis and 144 of pharyngitis.

2. As far as could be ascertained, none of the patients admitted prior to September 27 returned later suffering from the more severe type of illness.

3. There was no further sharp increase in the number of cases.

4. There was no sudden increase in the fatality of the cases occurring after that date. However, he says it is not only possible, but probable, that one or more new infections were superadded to the original infection at the time mentioned above.

5. Cases of the milder type returning to quarters from hospitals, while seem-

ingly immune to infection with the more severe type of the disease, were followed by the development of cases of the latter type. One instance occurred in the 14th Ammunition Train, where J. L. was sent to the Base Hospital on September 20. He was discharged still coughing, on September 27, as having suffered from bronchitis. Believing the case to have been one of influenza, the surgeon had him cubicled in the corner of the barracks, and warned him to keep away from other men; but two cases developed in that corner of the barracks on September 29, with 20 more cases in the next three days.

6. There was a sharp increase in the number of pneumonia cases coincident with the rise in the influenza cases, and the two curves continued to correspond.

The most noteworthy symptoms were as follows: marked prostration, almost comatose somnolence, dull expression, flushed and often cyanotic face, relative absence of cough, and marked congestion of the mucous membranes, congested eyes, red throat, hemoptysis and epistaxis. The last-mentioned symptom was noted in 30 per cent of the cases in one command. The congestion of the conjunctiva and sclera was so characteristic that a diagnosis could be made even at a distance.

It was observed in many cases that individuals admitted with high temperature would often improve quite markedly after twenty-four hours and walk to the lavatory, but in a few days their condition would grow rapidly worse with the development of pneumonia. On the other hand, cases with moderate or low temperature would improve more slowly, but more continuously, and less frequently develop pneumonia. Although the onset of the attacks was sharp and sudden, yet an initial chill, or one on the development of pneumonia, was rarely or never observed. No rashes, skin eruptions, or other exanthems appeared.

The Streptococcus hemolyticus was present in 75 per cent of the cultures, the Bacillus influenzæ in about 1 per cent. The Bacillus influenzæ was found in only 8 per cent of the cases of influenza in the prepneumonia stage, as against 34 per cent of the Streptococcus hemolyticus, and 12 per cent of the pneumococcus. After the development of pneumonia the Bacillus influenzæ was found in 4 per cent, usually associated with the streptococcus, while the streptococcus was found in 26 per cent.

Pathologically the cases were pronounced bronchopneumonia, and it is believed that the lesions were due principally to the streptococcus. There was marked leucopenia.

Following the epidemic there was an increase in cases of tonsillitis, erysipelas and otitis. Empyema, which had occurred rarely during the summer, developed in 43 cases of pneumonia after October 17. There were 30 cases of otitis media at the Base Hospital during the month of October.

Sixty-four per cent of the men had been in the service only two months.

The 41st Field Artillery showed the greatest relative percentage, and the Quartermaster Corps the least. The increased prevalence of the disease in the first two months after enlistment has been ascribed to the larger proportion of unfit men in the service at that period; that is, unfit men who had not been weeded out.

Most surgeons reported that the rurals in their command suffered more

largely than urbans. It was thought by some that the crowding, due to a series of lectures on venereal diseases just about the time the epidemic appeared, gave opportunity for the wide dissemination of the contagion.

Three thousand six hundred thirty-three of the command were in tents. The morbidity per thousand in these was 129. Thirty-six thousand fifty-five were in barracks. The morbidity per thousand among those was 275. At first glance the lower morbidity of those in tents is striking. Going further into the matter, however, it is found that the entire morbidity of the Quartermaster Corps was very low.

Of the Depot Brigade, 2,881 were in tents, with a morbidity of 128 per thousand, while 3,824 were in barracks, with a morbidity of 134 per thousand.

During the month of September and the first part of October, the weather was splendid. Before the beginning of the epidemic all organizations in the Division were doing intensive work. The ration was liberal, the average consumption per man being between 4,000 and 5,000 calories.

One of the larger organizations did not promptly observe the regulations requiring that all mess kits and table equipment be properly sterilized. This may have played a part in the epidemic, and may be the reason the disease appeared so early and spread so rapidly in this particular organization. It was largely felt that the two blankets supplied were not enough, and that the men were cold at night.

Camp Custer is about five miles from Battle Creek, which has a population of about 32,000. The first cases in Battle Creek were reported on September 30. There was a sharp increase on and after October 3. It is improbable that Camp Custer owed its outbreak to Battle Creek.

—*V. C. V.*

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ORIGINAL ARTICLES

THE LESIONS OF THE RESPIRATORY AND GASTROINTESTINAL TRACTS PRODUCED BY MUSTARD GAS (DICHLORETHYL-SULPHIDE)*

BY ALDRED SCOTT WARTHIN, PH.D., M.D., AND CARL VERNON WELLER, M.S., M.D., ANN ARBOR, MICH.

I. LESIONS OF THE RESPIRATORY TRACT

THAT irritation and inflammation of the upper respiratory tract, terminating in pneumonia, can be experimentally produced in animals by mustard gas was demonstrated in 1886 by Victor Meyer, the discoverer of this chemical entity. After its introduction into military use by the Germans, in the present war, the irritant effects of mustard gas upon the mucous membranes of the respiratory tract were noted by medical observers in the Allied Armies. The earlier British Army reports describing the respiratory symptoms produced by exposure to mustard gas speak of an initial tendency to sneeze, with gradually increasing nose and throat irritation, followed in about twelve hours by a free discharge of mucus from the nose. Prolonged exposures, even to slight concentrations, were observed to cause laryngitis and aphonia, even severe enough to put the men out of action. In the more severe cases bronchitis and pneumonia were found to develop thirty-six to forty-eight hours after the exposure. Ulceration of the mucous membranes of the respiratory passages may be so extensive and severe as to cause death in themselves or a fatal bronchopneumonia may follow. About 95 per cent of the men gassed with mustard gas showed involvement of the respiratory tract.

Giraud (*Journal de Médecine et de Chirurgie Pratiques*, 1917, lxxxviii, 890)

*From the Pathological Laboratory, University of Michigan, Ann Arbor, Michigan.

found that symptoms of involvement of the respiratory tract in the form of aphonia, coughing, tracheitis and bronchitis were, next to the eye lesions, the most common affections produced by exposure to mustard gas. *Mandel and Gibson* (*Journal American Medical Association*, 1917, p. 247) describe the respiratory symptoms of mustard gassing as an "irritative, noninflammatory, nonfebrile" laryngitis and bronchitis, with a feeling of constriction about the larynx, tightness of the chest, aphonia, and paroxysmal cough, particularly severe at night, with a serous discharge in the mild cases, hemorrhagic expectoration in the most severe, and purulent in the late stages complicated by bronchopneumonia. The physical signs are those of a diffuse bronchitis. The chief complications are pulmonary edema and a relatively late bronchopneumonia.

Pissarello (*Giornale di Medicina Militare*, 1918, lxvii, p. 128) describes the respiratory affections in mild cases of mustard gassing as coryza, dryness of throat and hoarseness, while in the more severe cases the hoarseness may pass into complete aphonia, with congestion and tumefaction of the pharyngeal mucosa, swollen uvula, and spots of whitish-gray exudate over the pharyngeal mucosa. He noted a laryngotracheitis only in the most severe cases, with occasional extension to the bronchi, with rales, or the production of atelectatic areas. In only two cases did he find a bronchitis with subfebrile state.

Rendu (*Lyon Médical*, March, 1918, p. 108) gives the most complete clinical description of the lesions of the upper respiratory tract caused by exposure to mustard gas, with a series of figures showing the location of the lesions in the nose, pharynx and larynx. The nasal symptoms were coryza lasting from one to five days, with a serous discharge, and epistaxis in one-eighth of his cases, and very frequently a diminution or complete loss of the senses of taste and smell. Rhinoscopic examination showed usually only a congestion of the mucosa, but in some cases small whitish ulcers were present at the level of the anteroinferior portion of the septum, or at the head of the inferior turbinate. The chief symptom referable to the pharynx was dysphagia, appearing usually about the second to third day and lasting about four to six days, but in some cases more severe and of longer duration. The objective symptoms were redness of the mucosa accompanied by a turgescence of the uvula and the posterior pillars. In about 15 to 20 per cent of the cases seen, localized whitish diphtheritic necroses were noted upon the pharyngeal mucosa, particularly upon the uvula and the neighboring borders of the pillars, but also on the posterior pharyngeal wall in its median portion, or behind the posterior pillars. In the most severe cases the diphtheritic eschars covered the entire posterior wall of the oropharynx and the laryngopharynx. Rendu found laryngotracheal symptoms to be the most common manifestation of the action of mustard gas in the upper respiratory tract. The subjective symptoms were sensations of tickling, dryness or burning, localized in the region of the larynx and behind the sternum, lasting for several days or weeks according to the intensity of the lesions of the mucosa. Coughing was constant and very painful, appearing about the same time as the laryngeal symptoms just described; it was dry, paroxysmal and was most troublesome at night. In about one out of ten cases there was for several days a blood-streaked expectoration. The voice was rough or husky

in 60 to 70 per cent of cases, and a complete aphonia occurred in about 30 to 40 per cent. The vocal symptoms disappeared very slowly as a rule. Rendu observed no symptoms of laryngeal spasm or edema. The laryngoscopic examination showed changes in the laryngeal mucosa ranging from a more or less marked hyperemia, accompanied by a tumefaction of the arytenoids and ventricular bands and the folds of the posterior commissure, to the development of whitish eschars, like those in the pharynx, localized at different places in the mucosa. He describes the development of the eschars as follows: During the first three or four days only the hyperemia of the mucosa is noted; the laryngoscopic examination is often difficult because of the abnormal intensity of the pharyngolaryngeal reflexes. From the fourth to the seventh day the necrosis of the mucosa begins to show in grayish or whitish patches resembling a false membrane. These eschars were observed most frequently at the vertex of the arytenoid pyramids, the border of the epiglottis, and the free border of the vocal cords, associated as follows: epiglottis and arytenoids, cords and arytenoids, and epiglottis, cords, and arytenoids. The most frequent lesions of all were the isolated eschars of the vocal cords which were arranged symmetrically on the anterior two-thirds of the free borders of the cords in the form of an elongated segment, sharply delimited on its external border, but somewhat irregular on its internal. The eschars are creamy white in color, while the remainder of the cord is deep red. The healing of these lesions is very slow, and requires several weeks. The *tracheal* lesions are analogous to those of the larynx; their subjective symptoms are more or less confounded with those of a bronchitis so often coexistent with it.

In the few reported autopsy findings in cases of death resulting from mustard gas the lesions of the respiratory tract are not very fully described. *Canelli*, in one case, observed a diffuse tracheitis, bilateral subacute bronchitis, pulmonary hypostasis with acute diffuse edema, and a localized fibrinoadhesive pleuritis. *McNee*,* in summing up autopsy findings, states that the respiratory tract lesions were acute inflammation of the air passages, desquamation of the mucous membranes and formation of false membrane, to which may be added infection in the form of acute purulent bronchitis, with atelectasis and bronchopneumonia. Emphysema may also be present. *Dunn** in four autopsies found the chief lesions to be severe damage to bronchi and bronchioles, persistent edema, and severe infection of respiratory tract, bronchopneumonia, and in two of the cases, hemorrhagic exudations. *Karsner* (*American Journal of Medical Sciences*, 1918, clv, 904) noted the following respiratory lesions in four autopsies following death from mustard gassing: Mucous membranes of nose and pharynx were the seat of a marked mucous inflammation. Larynx, trachea and bronchi showed severe inflammation, in one case with pseudomembrane formation, in two others with multiple necroses of the mucosa. In two cases there was an acute fibrinous pleurisy. All cases showed a bilateral bronchopneumonia with slight general edema of the lungs. *Rendu* records that in two autopsies the laryngotracheal mucosa, completely necrosed, was detached in shreds like a false membrane.

The animal experiments of *Kolls* and *Gilbert*, *Raper* and *Ball*, *Marshall*

*For references, see Jour. Lab. and Clin. Med., 1918, iii, No. 8, p. 454.

and *Miller,** and others have shown that mustard gas produces in exposed animals coryza, pharyngitis, salivation, tracheal rattle, congestion of the tracheal mucosa, bronchitis and bronchopneumonia. In the *United States Naval Bulletin,* April, 1918, there are some color plates of the gross pathologic changes in trachea and larynx of a dog dying forty-eight hours after a thirty-minute exposure to a 0.13 milligram-liter concentration of mustard gas. Edema and congestion of epiglottis and glottis, and an acute membranous tracheitis are shown. A section of lung from another dog shows atelectasis and patches of focal pneumonia following a thirty-minute exposure to 0.056 milligram-liter concentration. Plate V shows similar tracheal and pulmonary conditions.

The pathologic changes in the respiratory tract described above are chiefly those noted in clinical and gross pathologic observations. At this time no published reports in the general literature exist in which the detailed microscopic pathology of the respiratory tract lesions of dichlorethylsulphide gassing are given. It is the object of this paper to present such a statement of the minute pathology of these lesions, in such a way as to give a complete picture of the process from the mildest type of lesions to the most severe.

METHOD

In our gassing investigations we have made use of a simple apparatus, which has served our purposes most effectively and is to be recommended for its

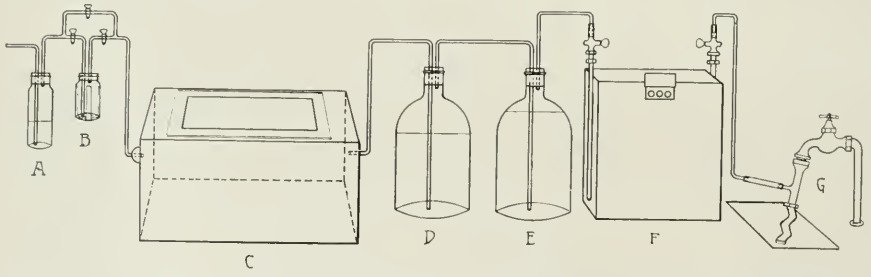

Fig. 1.—Experimental Gassing Apparatus. (Pathological Laboratory—University of Michigan.) A, Washer containing sulphuric acid; B, Gas container; C, Gassing box; D and E, Degassing bottles; F, Standard gas meter; G, Suction pump.

simplicity, as well as for the relative accuracy with which the gas concentration can be estimated. As shown in Fig. 1, it consists of:

A, one or more bottles containing sulphuric acid for drying the air admitted.

B, a container for the liquid mustard gas so arranged as to be easily detached from the tubing, so that when stoppered with a ground glass stopper, it can be weighed with its contents. Above this is a shunt tube for varying the amount of pure air admitted to the chamber, thus varying the concentration of gas obtained. Within the mustard gas bottle strips of absorbent paper are so arranged as to increase the evaporation surface. When used for experimental work with toxic substances, which are gaseous at room temperature, the gas intake replaces this weighing bottle.

C, a gassing chamber which is large enough to hold several small animals

*For references, see Jour. Lab. and Clin. Med., 1918, iii, No. 8, p. 454.

or a large dog. It has a removable plate glass top, so that the animals can be observed during gassing; this is sealed during the experiment with the gutta-percha-tallow mixture, commonly used for making air-tight seals for museum jars, and may be held in position by a heavy weight, if necessary.

D and *E*, bottles for removing the gas from the air flowing from the chamber, so that the amount passing over can again be estimated here if desired. When used for mustard gas these bottles may contain a chlorinated solution for the destruction of the gas.

F, a standard gas meter for measuring the amount of air passing through the chamber.

G, a suction pump attached to the city water supply.

After detaching the weighing bottle air is drawn through the gassing chamber for some time in order to wash out the mustard or other gas remaining. The weight of mustard gas used is obtained by difference and the amount of air drawn through during the period in which the bottle is attached is recorded from the gas meter. The concentration represented by these figures is obtained by reference to a transformation table. The results are as approximately correct as can be obtained by any other form of gassing chamber, and the apparatus has the advantage of simplicity. As far as mustard gas is concerned, such factors as variable absorption by the hair of the animal, etc., introduce unavoidable errors, so that absolute accuracy of method can not be obtained, regardless of the limitations of the apparatus.

The animals were killed by direct blow upon the neck to avoid the changes in the respiratory system produced by an anesthetic. Autopsies were made as quickly as possible after the death of the animal. The tissues were fixed in formol, were embedded in paraffin and the usual stains, hematoxylin and eosin, etc., were employed.

GROSS AND MICROSCOPIC PATHOLOGY

Various series of animals were exposed to varying concentrations of mustard gas in the gassing chamber for varying periods of time. It was found that rabbits would survive a forty-minute exposure to a dilution of 1:110,000, recovery taking place after a period of respiratory involvement. For purposes of brevity typical protocols have been selected and are given here.

Rabbit 32.—Exposed in the gassing chamber for forty minutes to a 1:110,000 concentration. During the gassing the rabbit frequently changed position, rubbed its nose, and showed signs of irritation. When removed from the gassing chamber the rabbit appeared unaffected in any way. In two and one-half hours conjunctival erythema and increased lacrimation were evident, these symptoms increasing until the animal was killed. Seven and one-half hours after removal from the box, symptoms of coryza manifested themselves. Twelve hours after removal from gassing chamber, rabbit was killed by blow upon the neck. The conjunctivæ presented marked congestion and edema, and were covered with purulent flakes. The bulbar conjunctivæ showed a marked collar of edema at the limbus. The cornea showed a slight haziness, and at its vertex there was a definite necrosis of the superficial epithelium. This area was irregularly oval in shape. The lid margins showed marked congestion and the skin about mouth and nostrils was erythematous.

Autopsy showed right-sided dilatation of the heart. No fluid was found in the pleural cavity, and there were no pleural changes. On section the lungs showed marked congestion and edema without hemorrhages or atelectasis visible to the naked eye. No

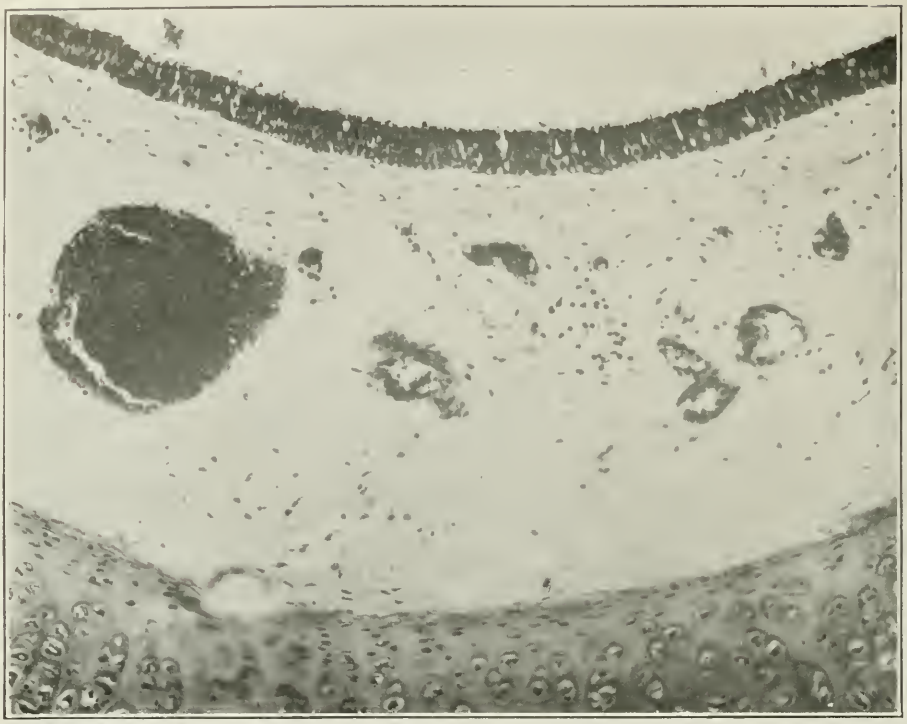

Fig. 2.—Section of laryngeal mucosa, Rabbit 31. Exposed thirty-five minutes to a concentration of 1:30,000. Killed thirty hours after gassing. Pyknosis and mucoid degeneration of the epithelium. Marked congestion and edema of the submucosa.

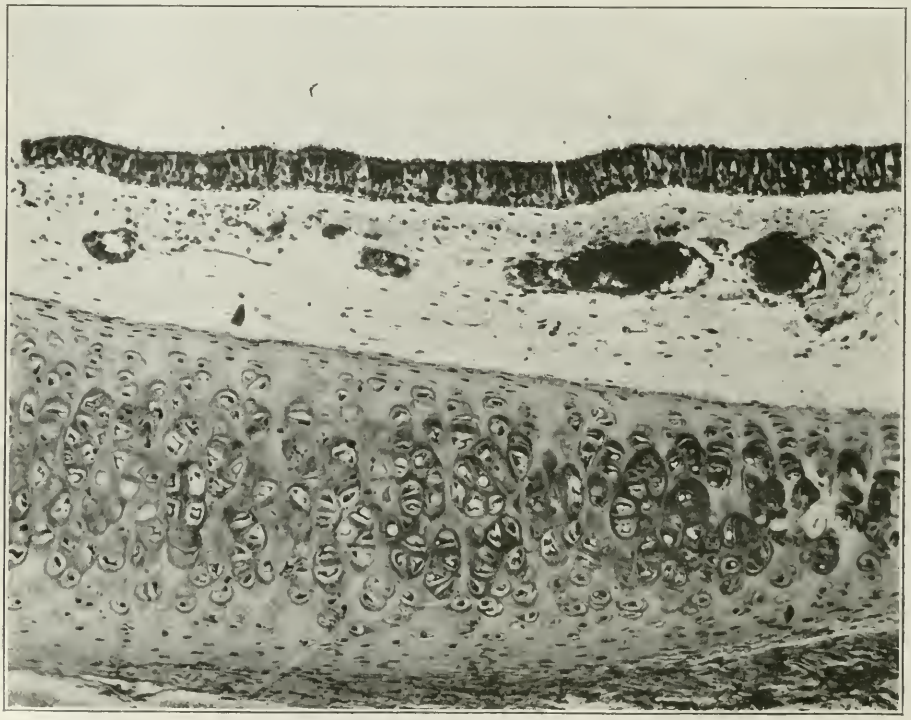

Fig. 3.—Section of tracheal wall of same rabbit as Fig. 2. Similar changes in epithelium and submucosa.

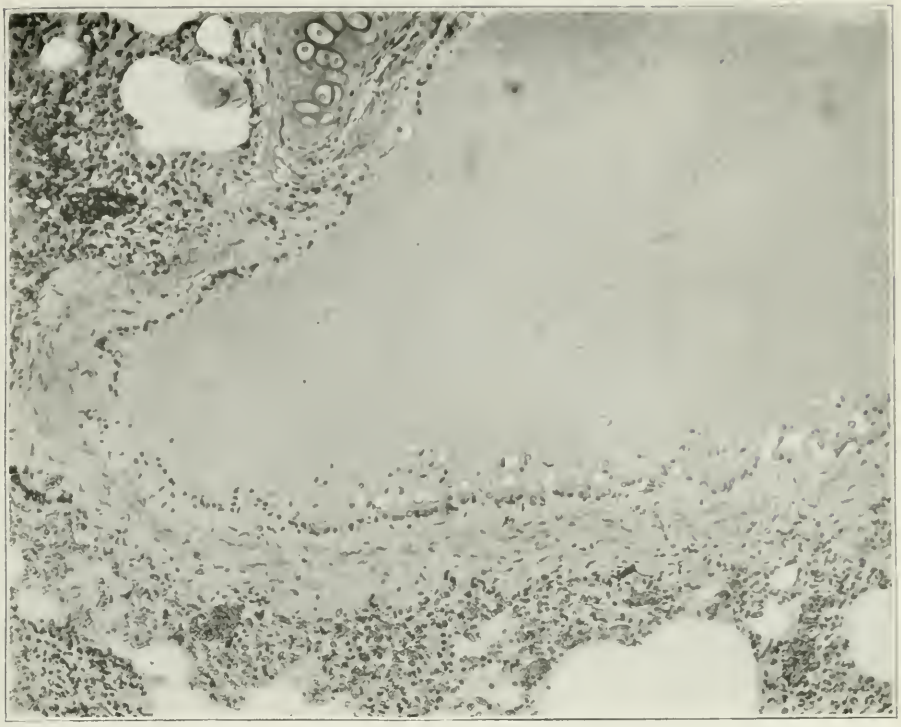

Fig. 4.—Rabbit 30. Exposed thirty minutes to a concentration of 1:15,000. Killed four and one-quarter days after gassing. Section of larger bronchus showing lumen filled with edema fluid. Bronchial epithelium shows marked mucoid and hydropic degeneration.

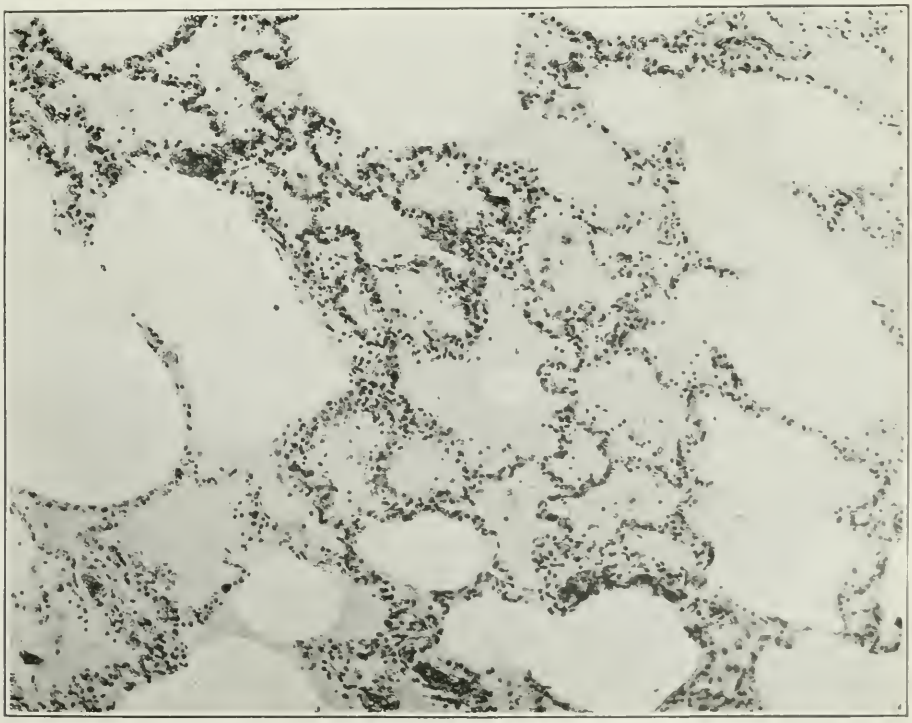

Fig. 5.—Lung of same rabbit as Fig. 4. Acute congestion and edema.

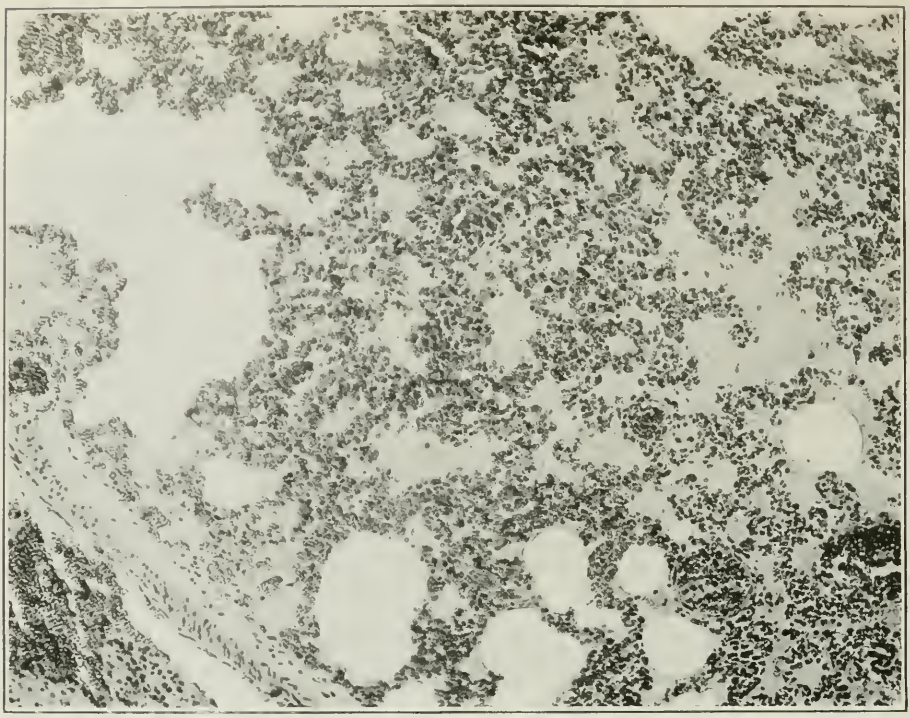

Fig. 6.—Rabbit 32. Exposed forty minutes to a 1:110,000 concentration. Killed twelve hours after removal from gassing chamber. Section of lung. Marked congestion, edema, and areas of partial atelectasis alternating with those of emphysema.

Fig. 7.—Rabbit 33. Exposed twenty minutes to a concentration of 1:15,000. Killed thirty-six hours after gassing. Section of trachea showing acute catarrhal desquamative tracheitis; marked mucoid degeneration of the epithelium; congestion and edema of the submucosa. Lumen filled with mucus containing many desquamated cells.

differences between upper and lower lobes were noted. The trachea was filled with frothy mucus and the mucosa was congested, particularly in the upper portion, the congestion diminishing below toward the bronchi. The mucosa of the entire upper respiratory tract, nose, mouth, pharynx and larynx showed congestion without hemorrhages.

Microscopic Findings. Nose. Sections from the skin about the nostrils show slight pyknosis of the epidermis and congestion of the vessels, without other changes. The mucous membrane of the nose shows a marked congestion, more marked pyknosis of the epithelium and slight edema. Sections from the *pharynx and larynx* show a marked congestion with extreme mucous degeneration of the mucous glands. There is pyknosis of the upper layers of epithelium of the mucous membrane but no definite necrosis. The acini of the mucous glands are greatly enlarged and filled with deep blue-staining mucus. The ducts are dilated and filled with mucus. There is but slight edema of the mucous membrane and no hemorrhages. These signs diminish in the *trachea* except for the edema, which is somewhat greater in the lower part of the trachea than above, and there is an increased number of wandering cells in the mucosa. The columnar cells of the tracheal mucosa show more marked changes than the squamous epithelium of the upper respiratory tract. The great majority show a hydropic or a mucoid degeneration. The epithelium is intact for the greater part but small patches of desquamation occur. The larger *bronchi* present the same appearance as the trachea, though to a somewhat lesser degree. The smaller bronchi are filled with mucus. The epithelium shows mucoid degeneration and occasional areas of desquamation. The walls of the larger bronchi are edematous, the vessels markedly congested, but there is no increase in leucocytes. The exudate in the bronchi is entirely mucoid or albuminous in character, not fibrinous. There is no hemorrhage into the bronchi. The *lung* tissue shows extreme congestion and marked edema, with numerous minute hemorrhages, too small to be seen with the naked eye (see Fig. 6). A majority of the alveoli are filled with a heavy albuminous precipitate, but scattered throughout the lung are numerous emphysematous alveoli and dilated bronchioles. No areas of complete atelectasis are seen, although edematous areas show partial collapse.

The changes in the respiratory tract of this animal are those of an acute catarrhal rhinitis, pharyngitis, laryngitis, tracheitis and bronchitis, decreasing somewhat in intensity from above downwards, with pulmonary congestion and edema.

Rabbit 33.—Exposed twenty minutes to a concentration of 1:15,000. During the exposure the rabbit changed its position from that of facing the inflowing mustard gas to the opposite direction. Three hours after removal from the gassing chamber the animal showed increased lacrimation in both eyes. The borders of the eyelids, skin areas about the mouth and nostrils, the ears and all parts of the body where the hair was short and thin exhibited a marked erythema. The animal showed marked photophobia and irritation of the eyes. Eight hours after removal from the chamber flakes of purulent material were seen over the conjunctivæ and a definite coryza had developed. The conjunctivæ were edematous and congested. These symptoms increased for thirty-six hours, when the animal was killed.

Autopsy showed a severe conjunctivitis and coryza. Right-sided dilatation of the heart. The upper air passages were filled with foamy exudate and the mucosa was congested. Pleural cavities and pleuræ negative. The lungs were markedly congested, the right lung more so than the left. The lungs appeared air-containing throughout, except for the midddle lobe on the right, which was solid in areas, dark red in color. On section it bled but slightly. Beyond congestion no other changes were found in any organs or tissues.

Microscopic Findings.—The cutaneous borders of the *nostrils* show necrosis, edema, congestion and marked leucocyte infiltration of the corium. The mucous membrane of the nose presents patches of necrosis of the epithelium, congestion and edema, areas of small-celled infiltration of the submucosa, and marked mucous degeneration of the mucous glands. *Mouth and pharynx.* Sections of tongue and pharyngeal wall show a contraction of the upper half of the squamous epithelium with pyknosis of the nuclei, congestion of the vessels, slight edema of the submucosa and slight small-celled infiltration. The *larynx* presents patches of necrosis in the hyperemic mucous membrane with marked edema extending to the cartilages. Small-celled infiltration is well marked. Mucous glands

show marked mucoid degeneration. The surface of the mucosa of the *trachea* is covered with patches of mucus containing desquamated cells. The epithelium shows marked mucoid and hydropic degeneration; there are large areas of complete necrosis with desquamation. In the submucosa there is a marked edema extending to the cartilage rings. The vessels are markedly congested (see Fig. 7). The larger *bronchi* show marked degeneration and necrosis, and desquamation of the epithelium, the epithelium being represented for the greater part by a single line of nuclei at the base. Many of the bronchi are filled with an exudate of mucus containing many desquamated and degenerating cells but few leucocytes. There is some edema of the walls of the bronchi and the number of leucocytes is increased around the bronchi. The smaller bronchioles show a better preserved mucous membrane but many of the cells are vacuolated, presenting mucoid or hydropic degeneration, and desquamation is frequent. The *lung* shows practically the same picture as in the preceding; marked congestion and edema, small hemorrhages into the alveoli and emphysematous alveoli and dilated bronchioles. Many of the edematous areas show partial atelectasis. The apparently solid area from the right lung presents a more marked atelectasis and a greater degree of edema but no pneumonia. Other organs show marked congestion without other changes.

The microscopical picture in this case is similar to that in the preceding, but the changes are somewhat greater in intensity with a greater degree of necrosis and a well defined leucocyte reaction.

Rabbit 30.—Exposed thirty minutes to a concentration of 1:15,000. Killed four and one-quarter days after removal from the gassing chamber. Within five minutes after removal from the box the animal showed the first signs of irritation, rubbing its eyes and nose frequently. Six hours afterwards there was a well-developed conjunctivitis. By twenty-four hours the conjunctivitis had greatly increased with marked conjunctival edema, and the animal showed a marked bilateral coryza. By the second day the snuffles and coryza were much worse, the animal showing a marked respiratory wheezing, audible several feet away. The conjunctivitis had become distinctly purulent in character, with multiple subconjunctival pin-point hemorrhages, extreme edema and beginning corneal ulceration. Throughout the day the snuffles and wheezing greatly increased, the animal appeared sick, restless, with respirations greatly increased and shallow, these symptoms reaching their height in the evening of the second day. From the morning of the third day the respiratory symptoms gradually improved until the animal was killed, four and one-quarter days after gassing.

Autopsy.—The eyes showed a very severe purulent conjunctivitis with characteristic porcelain appearance of the cornea. The mucosa of upper respiratory tract showed marked congestion and edema and mucous exudate diminishing in intensity from the nostrils to the nasopharynx. In the anterior two centimeters of the nasal tract the exudate was purulent in character. The nasopharynx, larynx and trachea presented marked congestion of the mucosa, and the lumen of the trachea was filled with a frothy mucus extending into the bronchi. No hemorrhages or ulcerations were seen in the mucosa of the upper respiratory tract. Pleural cavities and pleuræ were negative. The lungs were uniformly markedly congested and apparently air-containing throughout. No pneumonic areas or hemorrhages could be felt or seen. The heart presented a marked right-sided dilatation. Beyond a marked congestion, other organs and tissues showed nothing.

Microscopic Findings.—Nose. Sections from the anterior nostrils show a marked necrosis and ulceration of the mucosa with a marked edema and congestion of the submucosa and a polynuclear infiltration. Great numbers of staphylococci are seen on the necrotic mucosa. Throughout the submucosa are numerous minute hemorrhages by diapedesis, and in one medium-sized blood vessel, a definite thrombus. The mucous glands of the nose and nasopharynx present intense mucoid change. Sections from the *pharynx* show the squamous epithelium to be intact for the greater part, but the outer half is necrotic, dry, looking like stratum corneum. *Larynx.* The surface epithelium is completely necrotic in many areas, particularly where a mucoid exudate lies upon the surface. In other areas it is preserved, but has lost its columnar appearance, and is reduced to a layer of pyknotic nuclei staining almost black with hematoxylin. In the mucoid exudate in the lumen there are great numbers of swollen desquamated mucoid epithelial cells and very few leucocytes. The submucosa is edematous, the edema, however, being very irregularly distributed. The blood vessels show marked congestion and the number of

leucocytes in the submucosa is not increased. The laryngeal mucous glands show marked mucoid degeneration. Many of the larger *bronchi* are filled with mucus. The columnar cells show marked mucoid degeneration and pyknosis. Practically every cell is converted into a goblet cell. There is no increase of leucocytes in or about the bronchi. The pulmonary vessels show extreme congestion and in many of these are large masses of fibrin, irregularly scattered through the red blood cells, or at times somewhat laminated, presenting the appearance of recent thrombosis. Throughout the *lung* atelectatic areas alternate with emphysematous. The alveolar spaces of the atelectatic areas show marked edema, being filled with a pink-staining finely granular precipitate. The bronchioles in these atelectatic areas are distended and are filled either with a similar edematous fluid or a more mucous fluid. No pneumonic areas are found and no large hemorrhages. Minute hemorrhages by diapedesis are found along the walls of the greatly distended capillaries. The other organs show nothing but intense congestion. (See Figs. 4 and 5.)

The lesions are practically the same as in Rabbit 33, except that they are more severe in the nose and mouth. The purulent character of the nasal lesions is probably to be explained by the development of a secondary infection due to a staphylococcus.

Rabbit 31.—Exposed thirty-five minutes to a concentration of 1:30,000. On removal from the gassing box the animal showed some irritation of the eyes and nose. Four hours after removal the animal had developed a well-marked conjunctivitis with erythema of the exposed skin surfaces, and beginning snuffles with scant nasal secretion. Within twenty-four hours there was marked increase of the conjunctivitis and coryza. The animal was killed thirty hours after gassing.

Autopsy.—Eyes showed a marked conjunctivitis with purulent exudate. Exposed skin surfaces showed erythema and edema. The mucosa of entire respiratory tract from nose to bronchi showed congestion, slight edema, and abundant mucous exudate. Pleural cavities negative. Pleuræ negative. Lungs presented uniform congestion without consolidation, the lung tissue being apparently air-containing throughout. No hemorrhage or atelectatic or pneumonic areas visible to the naked eye. The heart showed dilatation of the right side. In other organs nothing notable but congestion.

Microscopic Findings.—Nose. Squamous epithelium of the anterior nostrils shows patches of complete necrosis, these minute erosions or ulcerations being covered with a fibrinopurulent exudate. The remaining epithelium shows more or less pyknosis. There is very little edema of the submucosa and no small-celled infiltration or hemorrhages. On the skin side of the nostrils the edema is more marked than on the mucosal side, and there is marked necrosis, pyknosis and desquamation of the epidermis. *Pharynx.* Squamous epithelium of mouth and pharynx shows patches of pyknosis, contraction of the upper third with pyknosis of the nuclei resembling cornification, congestion of the blood vessels, and slight edema of the submucosa. *Larynx.* The columnar epithelium shows marked mucoid or hydropic degeneration. The majority of the cells of the upper layer are either vacuolated or are goblet cells. The nuclei stain very heavily, but the epithelium is for the greater part intact, without desquamation. In the lumen there is a thin albuminous fluid containing very few desquamated cells, leucocytes, no fibrin, and but a small amount of mucin. The submucosa shows a rather marked edema with the leucocytes slightly increased. The vessels are markedly congested. The mucous glands show increased mucus formation. *Trachea.* The epithelium is intact throughout the greater portion, but shows mucoid and hydropic degeneration. The lumen is filled with a thin mucoserous fluid. Well-marked edema of the submucosa with some increase in leucocytes. Marked congestion of the vessels. *Bronchi.* The lungs present practically the same appearance as in the previously described cases but with less edema and on the whole a less marked congestion. The bronchi contain a smaller amount of fluid. The epithelium is better preserved, although showing mucoid change and vacuolar change in the larger ones. There is very little atelectasis, the *lungs* being rather emphysematous throughout. There is no pneumonia and no hemorrhage. The other organs show chronic congestion, the liver a chronic coccidiosis with cirrhosis. (See Figs. 2 and 3.)

In this rabbit the lesions in the anterior nares are severe, the degree of necrosis there being comparable to that on the conjunctiva and cornea, but the laryngeal, tracheal and bronchial lesions are of the mildest degree.

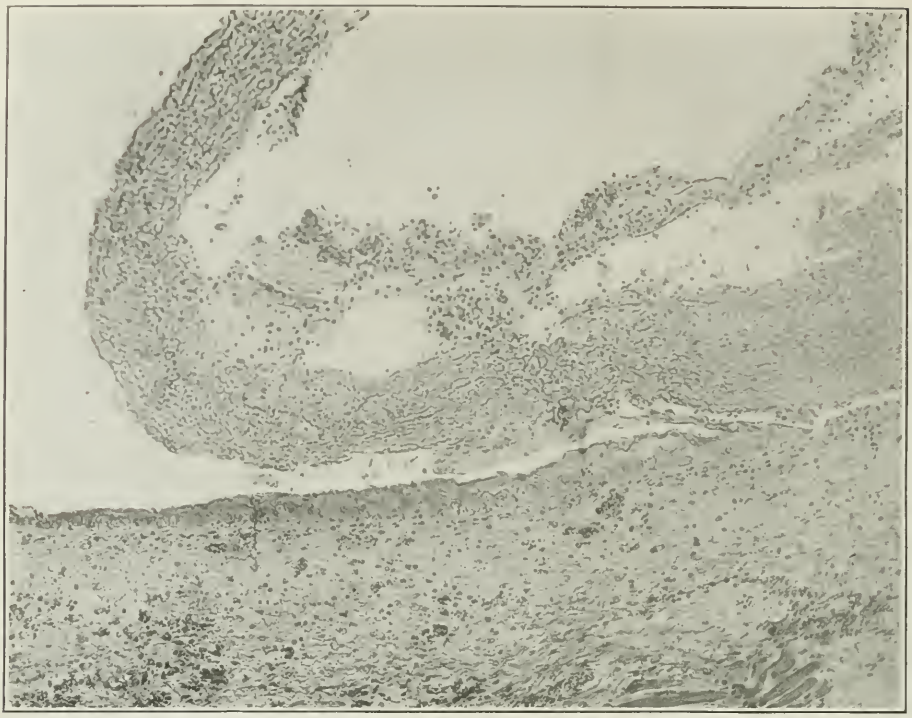

Fig. 8.—Rabbit 43. Exposed twelve hours to a concentration of 1:50,000. Died fifty-four hours after exposure. Section of tracheal wall, showing pseudomembrane in lumen and complete necrosis of the surface epithelium.

Fig. 9.—Section of large bronchus from same rabbit as preceding, showing diphtheritic necrosis of the mucosa. Early bronchopneumonia.

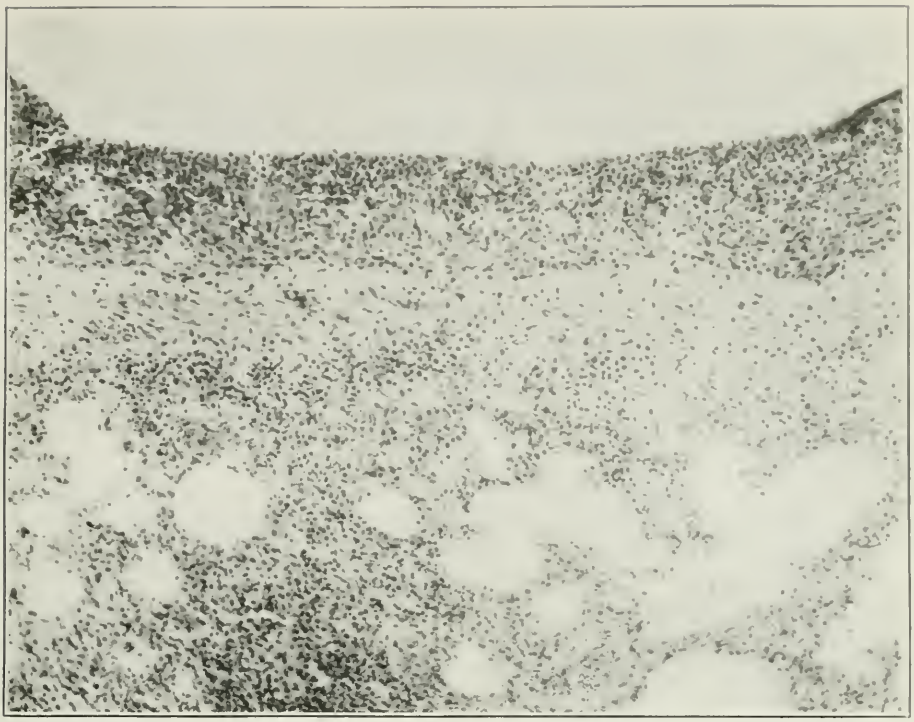

Fig. 10.—Rabbit 46. Exposed six hours to a concentration of 1:50,000. Died sixty hours after gassing. Section of large bronchus, showing purulent necrotic bronchitis.

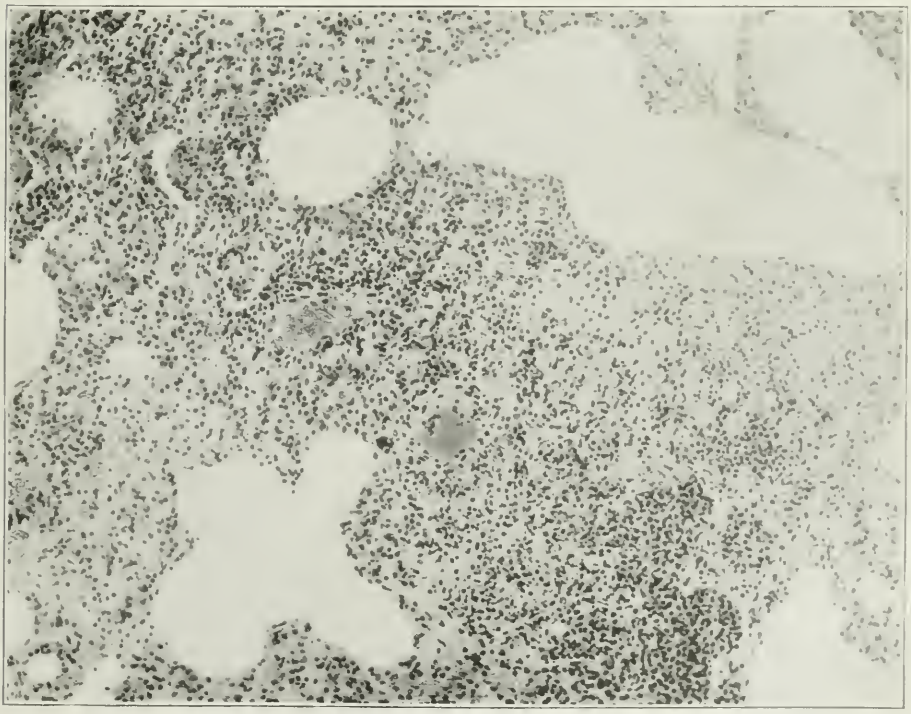

Fig. 11.—Section of lung from same case as preceding. Area of purulent bronchopneumonia with colony of cocci in the center of the field.

Rabbit 46.—Gassed six hours at a concentration of 1:50,000. Animal died sixty hours after removal from the gassing chamber. During the gassing the animal showed irritation within half an hour. At the end of an hour it became drowsy and was quiet with its eyes half closed. Within three hours there was a definite lacrimation and conjunctival edema, these conditions increasing during the remainder of the gassing. When taken from the box the eyes were very much congested, edematous and showed profuse lacrimation. By the next day the rabbit showed marked respiratory involvement, coughing all the time, and bubbling rales could be heard throughout its chest. These conditions increased during the next two days, the animal dying sixty hours after removal from the gassing chamber.

Autopsy.—Both eyes presented marked corneal opacity with mucupurulent conjunctivitis. Pharyngeal mucosa very markedly congested and edematous and covered with mucopurulent exudate. Buccal mucosa negative in appearance. Marked edema of all laryngeal structures and tracheal mucosa, the tracheal edema being most marked in the upper part, just beneath the larynx, where there were also small hemorrhages in the mucosa. Pleural cavities and pleuræ negative. Pericardial fluid increased, clear. Heart dilated; both sides filled with partly clotted blood. Both lungs were voluminous and air-containing without any airless areas except a small atelectatic area in the border of the lowest left lobe. On section the lungs showed moderate congestion and edema without any hemorrhages or pneumonic or atelectatic areas visible to the naked eye. Other organs showed no changes except congestion.

Microscopic Findings.—Nose. Anterior nares show a shrinking and pyknosis of the epithelium, the outer layers being desquamated and light staining, resembling cornified epithelium with pyknotic nuclei. In many areas this pyknosis and shrinking extends to the lowest layer of the epithelium. Through the lowest layer there are many hydropic cells and occasionally small vesicles are formed. The ciliated columnar epithelium shows a more marked necrosis, vacuolization and desquamation. There is marked edema of the submucosa extending to the cartilages and through the muscles. The mucous glands show extreme mucoid degeneration; the blood vessels, extreme congestion. There are minute hemorrhages about the mucous glands and the number of wandering cells is increased. The *buccal mucosa* and the *tongue* show necrosis of the upper half to two-thirds of the squamous epithelium, with partial desquamation of these dead cells in lamellæ. There is slight edema and moderate congestion of the subepithelial tissues. The mucosa of the *pharynx* shows the same changes with a more marked edema of the submucosa. *Larynx.* In the lumen, lying upon the surface, there is a fibrinopurulent membrane which is firmly attached in areas where the epithelium is completely lost. In these areas the picture is that of a diphtheritis. Colonies of staphylococci are present in the diphtheritic membranes and on the necrosed epithelium. Where the epithelium is preserved it shows marked vacuolation with hydropic and mucoid degeneration. In some areas the epithelium is still attached but is necrotic and infiltrated with polynuclears and eosinophile cells. There is a very marked subepithelial edema, extreme congestion of the blood vessels and areas of leucocyte infiltration, many of these being eosinophiles. This infiltration is most marked in the neighborhood of the diphtheritic areas. The cervical lymph nodes in this case show marked eosinophilia and great numbers of hemophages in the sinuses. *Trachea.* Mucosa of the trachea shows marked mucoid and hydropic degeneration. There is a diphtheritic necrosis, but the process is less marked than in the larynx. Edema and congestion of the wall are about the same. The epithelium of the larger *bronchi* shows marked degeneration and necrosis. There is an increase in leucocytes in the walls of the larger bronchi, the submucosa is edematous and the vessels are markedly congested. The majority of the smaller bronchioles contain a mucopurulent exudate and the bronchial wall is infiltrated with leucocytes. Around many of the bronchioles there are definite areas of a hemorrhagic purulent bronchopneumonia. Colonies of staphylococci are found in each of these areas. Between these areas the alveoli are overdistended and emphysematous. Other alveoli contain a heavy albuminous percipitate of edema. The *liver* presents a marked nutmeg liver, central necrosis and congestion of lobules. The *kidneys* show marked cloudy swelling and congestion. (See Figs. 10 and 11.)

The respiratory lesions in this animal are more pronounced than in any of the preceding, as is shown by the diphtheritic necroses in the larynx and trachea, the purulent bronchitis and bronchopneumonia. The cause of death

is considered to be an infective (staphylococcus) bronchopneumonia, secondary to the lesions produced by the gassing.

Rabbit 45.—This rabbit was gassed at the same time as Rabbit 46, in the same box for six hours at a concentration of 1:50,000. Its reaction during the gassing and afterwards appeared to be identical with that of No. 46, but the animal lived for seven days.

Autopsy.—The autopsy findings were the same as for No. 46, but the changes were more severe in character. The anterior nares showed extensive ulcers covered with diphtheritic membrane and the nasal cavity was filled with a mucoid fibrinopurulent membrane, this membrane extending through the nasopharynx and into the larynx and trachea. This membrane was in part firmly adherent to the wall, particularly along the posterior wall, while anteriorly it was loose and separated as a cast of the tracheal tube. Heart showed marked dilatation of both cavities. Pleurae and pleural cavities negative. Large bronchi filled with purulent exudate. Lungs voluminous, markedly congested and edematous, with the picture of a diffuse bronchopneumonia.

Microscopic Findings.—The microscopic examination of the *nose*, *nasopharynx*, *larynx* and *trachea* reveals the presence of a diphtheritic inflammation with a membrane containing numerous colonies of cocci. This membrane is firmly attached wherever the epithelium is completely lost, but is loose and separates from the surface wherever the epithelium is still intact. In the larynx and trachea a large part of the columnar epithelium is replaced by a regenerating layer of large deeply staining pavement or cuboidal cells. The submucosa shows marked congestion, edema, scattered hemorrhages and leucocyte infiltration. The larger *bronchi* are filled with a fibrinopurulent membrane which is adherent to the wall and contains many large colonies of cocci. The epithelium is entirely absent except in a few places where there is a regenerating layer. *Lungs.* The lungs present the picture of an advanced fibrinopurulent bronchopneumonia with large areas of consolidation. All the bronchioles appear as abscesses. In some of these there are many large epithelial giant cells, syncytial in type, showing an attempt at regeneration, but the great majority show complete destruction of the epithelium. Syncytial epithelial giant cells are also found in some of the alveoli. Colonies of cocci are found everywhere. Many of the pneumonic areas show older and fresh hemorrhages and marked inflammatory edema. (See Figs. 12 to 20.)

This case presents a more marked diphtheritic inflammation of the upper respiratory tract and a diffuse purulent bronchopneumonia due to secondary infection following gassing.

Rabbit 43.—Exposed for twelve hours to a concentration of 1:50,000. Died fifty-four hours after removal from the gassing chamber. In the first stages of the gassing the animal showed nasal irritation, but later became drowsy and depressed, and sat with eyelids nearly closed. At the end of two hours increased lacrimation and conjunctival edema were first noted. When removed from the gassing chamber there was a well marked conjunctivitis with coryza and salivation. The animal would not eat or drink but appeared stupefied. The coryza gradually increased in intensity and within six hours after removal from the chamber bubbling respiratory sounds were heard over its thorax. Coryza and conjunctivitis increased during the first twenty-four hours, at which time there was a profuse seropurulent nasal discharge. The wheezing and bubbling respiratory sounds could be heard some distance from the cage. Respirations were rapid and apparently difficult. Thirty-six hours after gassing the rabbit was still much depressed and the respiratory sounds were louder. The animal frequently sneezed and coughed. There was a marked purulent discharge from the eyes and nose. Forty-eight hours after removal from the gassing chamber the animal was very weak, the respiratory movements more rapid and much forced, the thorax heaving. Both eyes were sealed with a thick purulent exudate. After increasing respiratory difficulty the animal died, fifty-four hours from the time of exposure.

Autopsy.—Marked purulent conjuctivitis with corneal ulceration. Erythema of the exposed portions of the skin. Marked edema of the subcutaneous tissue, particularly in the region of head, neck and thorax. Nose filled with purulent exudate, the mucosa showing deep necroses. Nasopharynx filled with mucopurulent fluid. Larynx and trachea filled with frothy exudate beneath which there was a membranous cast, partly adherent but decreasing in intensity downwards. The mucosa of the entire upper respiratory

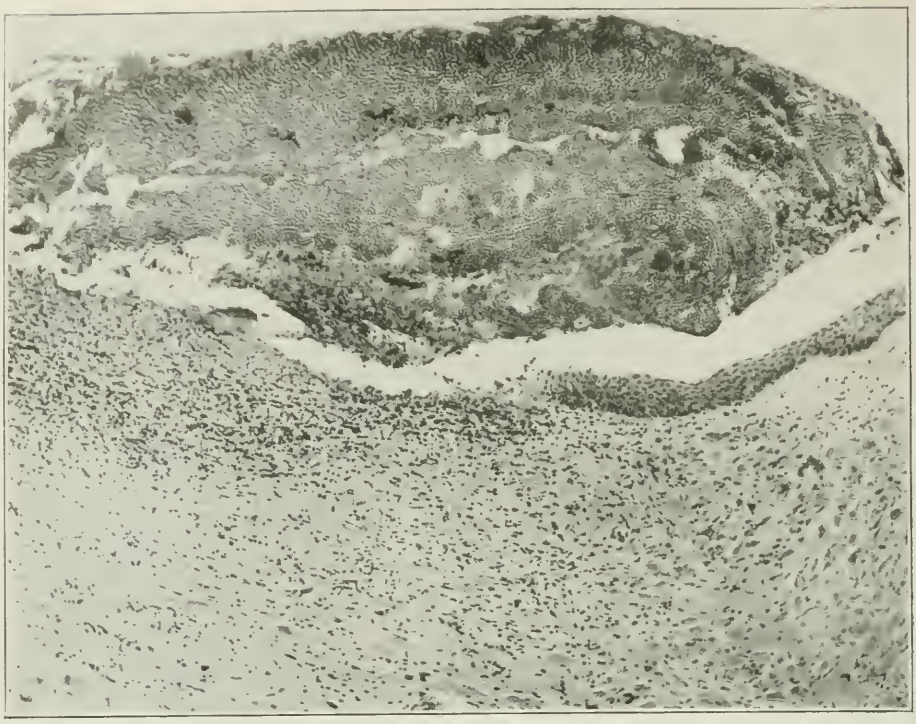

Fig. 12.—Rabbit 45. Exposed for six hours to a concentration of 1:50,000. Died seven days after gassing. Eschar from upper portion of larynx.

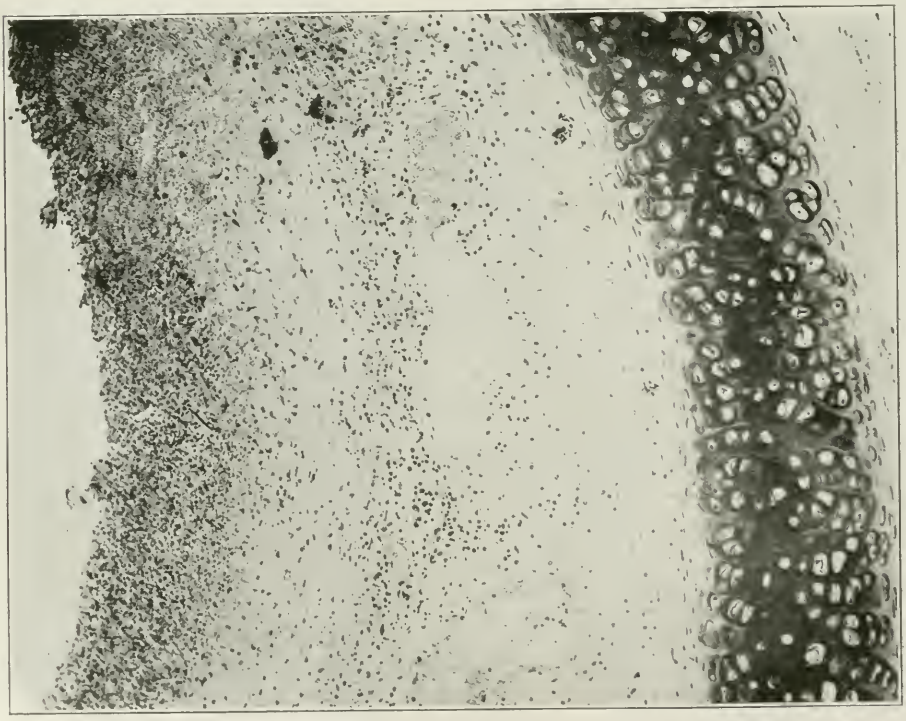

Fig. 13.—Same rabbit as preceding. Section of larynx showing diphtheritic ulcer.

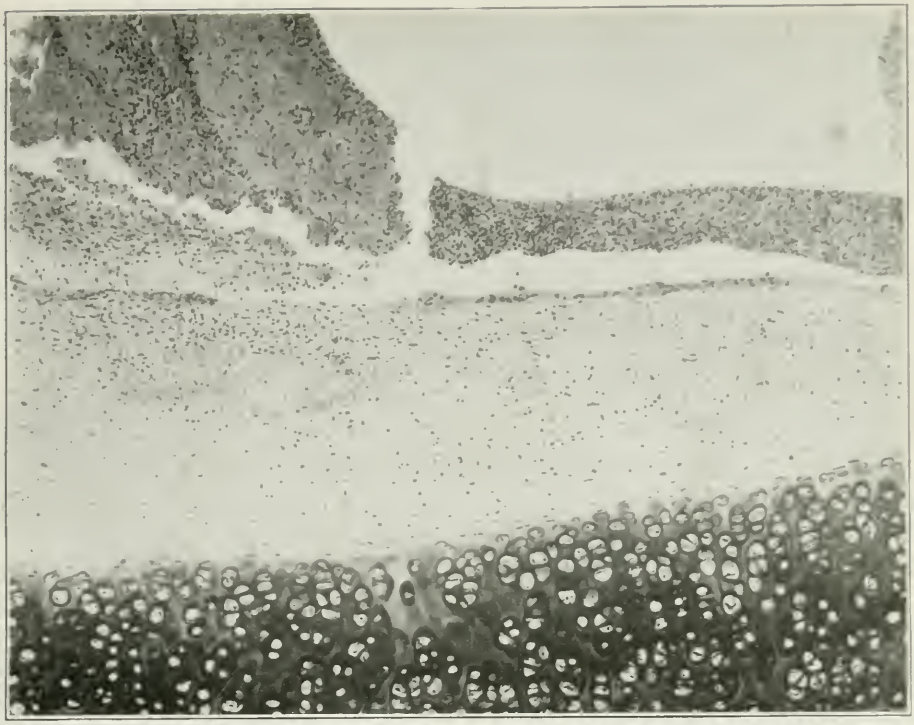

Fig. 14.—Same rabbit as preceding. Section of tracheal wall. Diphtheritic membrane. Epithelium in part gone and in part showing early regeneration. Congestion and edema of submucosa. Small-celled infiltration.

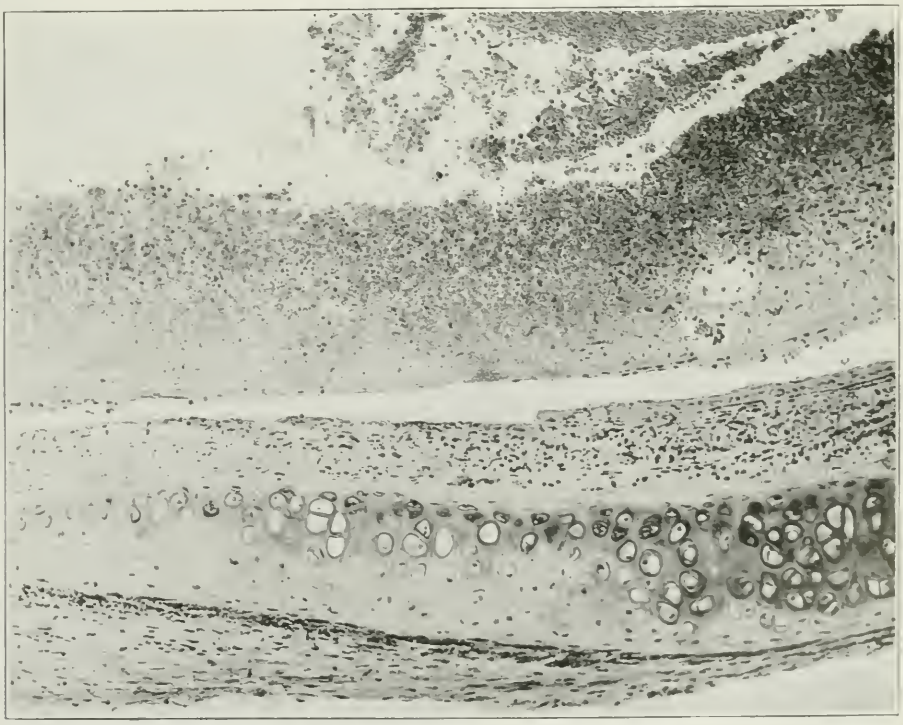

Fig. 15.—Same rabbit as preceding. Wall of large bronchus. Diphtheritic membrane. Complete necrosis of epithelium.

Fig. 16.—Section of medium-sized bronchus from same rabbit as preceding. Complete necrosis of bronchial epithelium; purulent exudate in bronchus. To the left of the congested vessel, colonies of staphylococci in the alveoli.

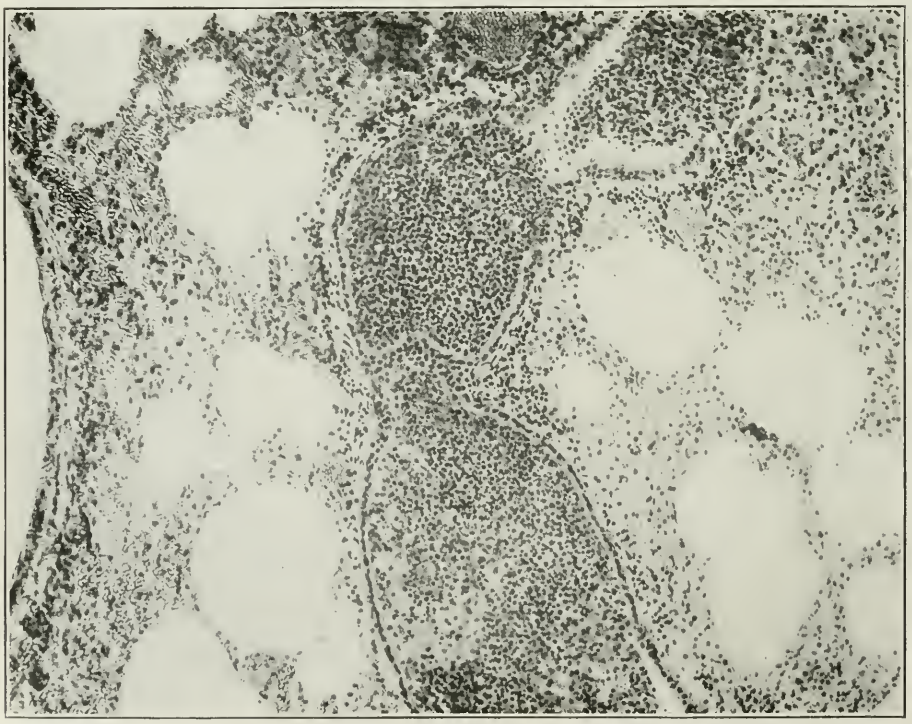

Fig. 17.—Section of lung from same case as preceding. Smaller bronchus filled with purulent exudate.

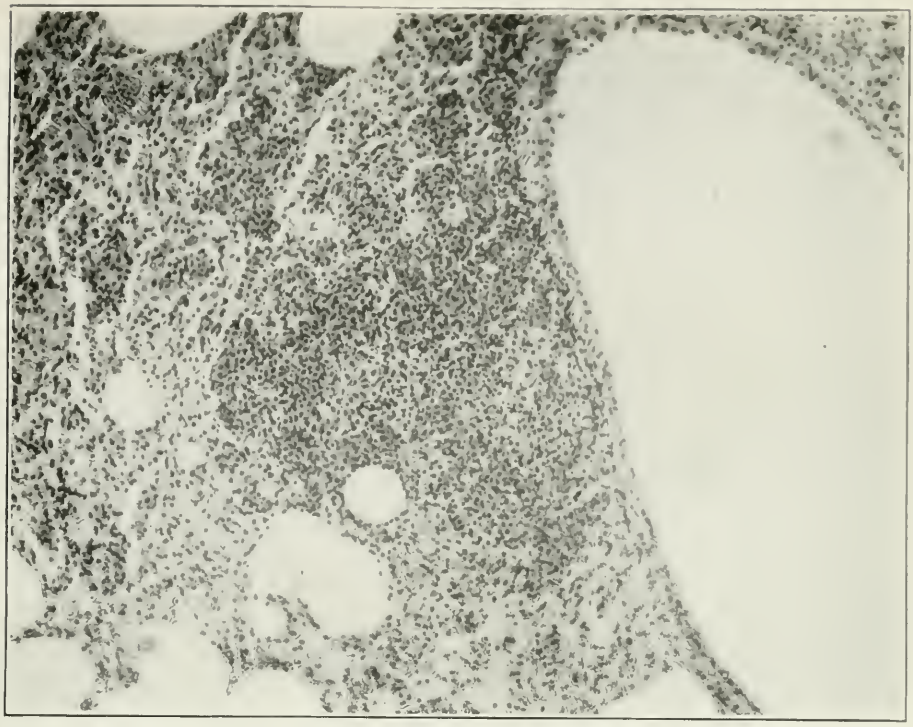

Fig. 18.—Section of lung from same case as preceding. Area of purulent bronchopneumonia with a dilated bronchiole showing necrotic epithelium.

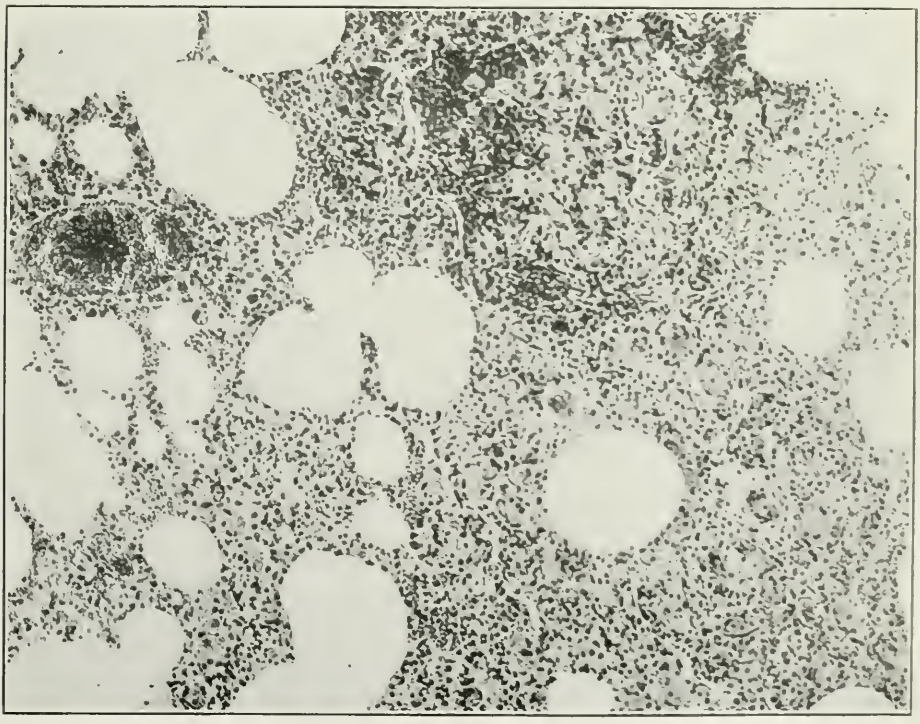

Fig. 19.—Section of lung from same case as preceding. Terminal bronchiole filled with pus and containing many regenerating epithelial cells. Large syncytial epithelial cells seen also in the neighboring pneumonic area.

tract was markedly congested and showed marked necrosis of the surface epithelium. The lungs showed marked congestion and edema. At the base of each lung there was an olive green area, the central portion of which was lighter in color. Bronchi filled with a thick mucopurulent exudate. Pleuræ were negative. Heart showed marked dilatation of the right ventricle. All other organs showed marked congestion. Some cloudy swelling in the kidneys. The external genitals were very erythematous and edematous.

Microscopic Findings.—The *nose* is filled with a diphtheritic fibrinopurulent exudate and the epithelium is completely necrosed, except for very small areas in the folds. The membrane is for the greater part adherent, but loosened in some areas. The submucosa shows marked congestion, leucocyte infiltration, and edema, extending into the muscles and cartilages. The mucosa of the *pharynx* shows a more marked necrosis of the squamous epithelium than in any of the above cases. The cells of the lowest layers are markedly pyknotic. The *larynx* and the *trachea* show a diphtheritic process, the surface being covered with a fibrinopurulent membrane which is firmly attached where the epithelium is entirely absent, but lying loosely on the surface where the epithelium is still intact or regenerating. In the membrane there are colonies of cocci. The epithelium of the larynx and trachea is reduced to a single layer of pyknotic nuclei over a large extent of surface. The submucosa shows marked fibroblastic proliferation, leucocyte infiltration and edema, with minute hemorrhages. The mucous glands of the larynx and trachea show some acini and ducts distended with mucus, but the greater number of the acini appear small, collapsed and pyknotic. The inflammatory infiltration and edema extend into the muscle. The mucosa of the upper part of the *esophagus* shows marked pyknosis and necrosis of the upper layers of the epithelium. The larger *bronchi* show a nearly complete necrosis of the epithelium and a fibrinous membrane adherent to the surface forming casts of the bronchial tubes. There is marked congestion of the wall and leucocyte infiltration of the surrounding tissues. The smaller bronchioles are filled with mucous and albuminous exudate with increased leucocytes. The epithelium is intact, but shows mucoid degeneration and pyknosis of the nuclei. A very few bronchi contain a mucopurulent exudate. The *lungs* show extreme congestion, numerous hemorrhages by diapedesis, a few small areas of early bronchopneumonia and atelectatic edematous areas beneath the pleura. The only bacteria found are those in the bronchioles containing the mucopurulent exudate. Marked congestion of all other organs. Cloudy swelling of the liver and kidney cells.

This case differs from the preceding in the severe diphtheritis of the upper respiratory tract with more marked evidences of healing in the larynx and trachea. It shows a severe secondary infective process of the larynx and trachea with less involvement of the bronchi and lungs.

Rabbit 44.—Gassed for twelve hours at a concentration of 1:50,000, at the same time with Rabbit 43. Reaction during the gassing identical. Developed a corresponding conjunctivitis and coryza with similar pulmonary symptoms. This animal, however, survived until 92 hours after the end of the exposure.

Autopsy.—Generalized mustard burn of the skin, especially where the hair was thin, in the form of a marked erythema, marked subcutaneous edema and dilatation of the superficial vessels. The untreated left eye showed a severe purulent conjunctivitis with corneal opacity and superficial ulceration. The right eye had been treated with dichloramine-T and showed a much less severe conjunctivitis and injury to the cornea. The upper respiratory tract was filled with frothy exudate. The mucosa, particularly of the trachea, showed a diphtheritic necrosis with membrane, most marked at the larynx and just below it, but extending into the bifurcation. Bronchi filled with frothy exudate. The lungs were voluminous, with marked congestion and very edematous on section. Atelectatic areas seemed to alternate with emphysematous. At the anterior border of the lowest lobe of the left lung, there was an area greenish gray in color, softened and apparently necrotic. Right ventricle and conus markedly dilated. All other organs congested. In the intestine, small necrotic areas, with inflammatory reaction about them, were found, the entire intestine being markedly congested.

Microscopic Findings.—*Nose.* Slough of the skin of the nose adherent. On the mucous membrane side an ulcer with slough adherent in some areas. Fibroblastic proliferation well developed. *Mouth.* Tongue shows numerous small areas of ulceration and sloughs extending down to the muscle. The remaining portion of the epithelium is intact but shows pyknosis and contraction of the outer half. *Pharyngeal* mucosa shows the same lesions.

Mucous glands of nose and nasopharynx show very marked mucoid degeneration. Intense congestion of the neighboring vessels. Patches of leucocyte infiltration. The *larynx* shows a purulent infiltration of the wall extending to the cartilages. A fibrinopurulent membrane is adherent to the surface over the greater portion and beneath the membrane there is a phlegmonous infiltration of the wall of the larynx. Small patches of epithelium upon the surface have the appearance of regenerating epithelium, regeneration taking place apparently from the ducts of the mucous glands. Numerous colonies of cocci are found in the pus. Below the larynx the epithelium is present over the greater part of the *tracheal* mucosa, which shows mucoid and hydropic degeneration. There are also islands of regenerated epithelium with some fibroblastic proliferation in the submucosa. The tracheal wall shows congestion, edema, small-celled infiltration and fibroblastic proliferation. The larger *bronchi* are filled with pus. Small diphtheritic areas are found on the mucosa, where the epithelium is entirely gone and the fibrinopurulent exudate is adherent. Walls of the bronchi are edematous, infiltrated with leucocytes, and the blood vessels are congested. Any epithelium remaining shows mucoid and hydropic degeneration. The *lungs* show extreme congestion and numerous small hemorrhages. The alveoli for the greater part are overdistended, emphysematous, although there are many small atelectatic areas in the neighborhood of plugged bronchi. The atelectatic areas show a marked edema. Practically all the bronchi and bronchioles are filled with a purulent exudate and around many there are areas of purulent bronchopneumonia. Colonies of cocci are found in the pus in the bronchi. Other organs show intense congestion. No other organs show changes, with the exception of stomach and intestine, in which small sloughs are found, probably the result of local action of mustard gas swallowed in food or saliva.

This rabbit shows a severe purulent and diphtheritic inflammation of the upper respiratory tract and a purulent bronchopneumonia, due to a staphylococcus, secondary to the more severe lesions caused by the gassing.

SUMMARY OF EXPERIMENTAL WORK

From repeated and carefully controlled animal experiments we have arrived at the following conclusions in regard to the production and nature of the respiratory lesions due to mustard gassing.

1. The respiratory lesions are proportionate to the concentration of mustard gas employed and to the length of exposure.

2. The mildest lesions are those produced by short exposures, such as ten to fifteen minutes, to dilutions of 1:110,000 or over; or very short exposures, one to several minutes, to higher concentrations.

3. Exposure to mustard gas causes almost immediate signs of nasal irritation on the part of the animal. It will almost immediately rub its nose and turn its back to the inflowing gas. Conjunctival symptoms, in the form of photophobia and increased lacrimation usually appear within two to three hours, the respiratory symptoms developing two to three hours later, as a rule, in the form of snuffles, increased nasal secretion or a more or less severe coryza. In the case of short exposure, or low concentration of the gas, the respiratory symptoms do not progress beyond a catarrhal stage.

4. In prolonged exposures, or exposures to higher concentrations, the respiratory symptoms appear at relatively the same time, but usually later than the conjunctivitis. They then increase in intensity for several days until a picture of diffuse diphtheritic inflammation of the respiratory tract is produced, as manifested by increasing difficulty in respiration, exudation, rales and coughing. The animal may die within forty-eight hours, or later.

5. The pathologic lesions in the mildest cases consist of a superficial de-

generation or necrosis of the epithelium of the mucous membrane, with congestion and edema and increased mucus secretion. These milder lesions are found chiefly in the anterior nares, the pharynx, larynx and upper portion of trachea; but animals killed after such exposures invariably show a more or less marked pulmonary congestion and edema, and increased bronchial secretion. From lesions of this degree, recovery, without secondary infection, usually takes place.

6. The severer lesions consist of deeper necrosis of the mucosa of the tract and the formation of a diphtheritic membrane in the anterior nares, nasopharynx, larynx, trachea and larger bronchi. The most severe lesions are always in the nares, pharynx, larynx and upper part of the trachea, the intensity decreasing toward the bronchi. The respiratory columnar epithelium suffers more than the epithelium of the mouth cavity, although irregular areas of complete necrosis of the latter may be produced. The entire epithelium of the larynx, trachea and larger bronchi may be killed outright and the surface covered with a diphtheritic membrane, which, for the greater part, is easily detached, forming a cast of the larynx, trachea and larger bronchi. The laryngeal and tracheal walls show edema, congestion and small-celled infiltration, but the edema is always less marked than in the case of the subcutaneous tissues or the conjunctivæ.

7. In the severe cases, secondary infection with staphylococci almost invariably occurs, and the lesions in the larynx, trachea and bronchi usually take on a purulent character within four to six days, if the animal lives that long.

8. In the mildest cases the lungs show congestion and edema with hydropic and mucoid degeneration of the epithelium of the bronchioles. In the more severe cases the necrosis of the epithelium extends into the smaller bronchial divisions and bronchioles and a secondary purulent bronchopneumonia, apparently usually due to staphylococci, follows. In these severer pulmonary lesions, atelectatic areas, due to the plugging of the bronchioles with exudate, usually alternate with emphysematous areas. The atelectatic areas are usually edematous or hemorrhagic. Secondary hemorrhage into the purulent bronchopneumonic areas is also frequent, in some cases the condition assuming the picture of a hemorrhagic bronchopneumonia. In the pneumonic areas following gassing, colonies of staphylococci are always present.

9. In the severe cases death may occur more quickly as the result of a diphtheritic or purulent laryngitis without the development of pneumonia, but in the majority of cases, the cause of death, so far as the respiratory tract is concerned, is the development of an infective purulent bronchopneumonia secondary to the injury produced by the gassing.

10. Cases with localized diphtheritic necroses in nose, mouth, larynx and trachea, without extensive bronchopneumonia, may recover with healing and cicatrization of these areas. Fibroblastic proliferation in such areas was noted as early as the fourth day after gassing. Cicatricial contractions of trachea or larynx may result from such healed lesions.

CLINICAL MATERIAL

The clinical features of mustard gas lesions of the respiratory tract in man were studied in the cases of seven soldiers who were severely gassed in the manufacture of mustard gas, although wearing gas masks. The concentration of the gas to which these men were exposed was so strong that all received severe burns, two of the cases terminating fatally. In addition to these severe cases, data were secured from 63 other workers with mustard gas who had had at one time or another milder respiratory symptoms following accidental exposure to mustard gas vapor.

Case I.—Private Ha. Exposed one hour in several shifts. Within a few hours after the exposure he developed erythema of the skin, nausea and vomiting and complained of intense thirst. This patient developed no conjunctivitis, his eyes being sufficiently protected by the gas mask. Later, burns about the lips appeared and within the next few days, diphtheritic necroses developed over the dorsum of tongue, uvula, hard and soft palate, pillars of fauces, tonsils and pharynx. On the seventh day after the accident, large moist rales were present over both lungs, and he was thought to have a diffuse bronchopneumonia. The patient died eight days after gassing. The autopsy report of his respiratory tract changes will be found below.

Case II.—Private S. Exposed three-quarters of an hour, in several shifts, to the same concentration as the preceding. During the next few hours, in addition to the development of conjunctivitis, nausea and vomiting and erythema of the skin, he complained of intense thirst, and later showed patches of diphtheritic necrosis on the lips, angles of mouth, hard and soft palate, uvula, pillars, tonsils, buccal surfaces, dorsum of tongue and gums. All of the mucous membrane of the mouth showed erythema and desquamation of the epithelium. When seen on the eighth day he could barely whisper and had physical signs of a diffuse bronchopneumonia. He died four weeks after the accident. Autopsy not permitted.

Case III.—Private Mc. Exposed forty minutes in four shifts. Within a few hours after the exposure, coincidently with the nausea and vomiting and erythema of the skin, he complained of a very dry throat. For three days he had a hacking cough and complete aphonia. The roof of his mouth was very painful and on the third day one of the sore places in his throat "seemed to burst" and he coughed up membrane-like material, after which his symptoms were improved, but his voice remained husky and a bronchial cough persisted for some time. When examined eight days after the accident he had a catarrhal rhinitis and patches of diphtheritic necrosis over the mucous membrane of the mouth, particularly on the right pillar and in the posterior pharyngeal wall. Occasional loud moist rales were heard over his thorax. Respirations increased.

Case IV.—Private W. Exposed one-half to three-quarters of an hour in two or three shifts. In the first few hours after the exposure he developed mouth and throat symptoms in the form of a dry sore throat and could barely whisper. When examined eight days after the accident he showed diphtheritic necrosis of the mucous membrane of the lips, angles of the mouth, hard and

soft palate, uvula, anterior and posterior pillars, tonsils and posterior pharyngeal wall. The roof of the mouth was covered with a grayish green diphtheritic membrane through which numerous discrete yellowish white elevations appeared, suggesting small pustules on erythematous bases. On the eighth day he developed symptoms of a diffuse bronchopneumonia from which he later recovered, after, in the meantime, having expectorated a fibrinous bronchial cast, containing streptococci.

Case V.—Private M. Exposed one-half hour in one shift. Had severe thirst but no soreness of mouth or throat. He developed a temporary erythema of the mucosa of the hard palate with a small patch of diphtheritic necrosis. Voice husky, frequent cough and respiratory rate increased.

Case VI.—Private E. Exposed ten minutes in one exposure. On the next day complained of a very dry throat. He showed only a temporary erythema of the mucous membrane over the hard palate. When seen eight days later his voice was husky, and he had an occasional dry cough.

Case VII.—Private Hu. Exposed ten to twelve minutes in one shift. He developed a severe rhinitis and a sore throat, but showed only an erythema of the mucous membrane of the mouth. When seen eight days after the accident, his voice was still husky, and he had a laryngeal cough.

A large number of other cases of mild respiratory lesions were also seen. All of these were in cases with conjunctivitis. These patients complained usually of a dry or sore throat, huskiness of voice with or without an accompanying rhinitis. A dry laryngeal cough usually persisted for several days, a definite huskiness for a longer period. In two cases, short exposures to weak concentrations produced in susceptible individuals a fibrinopurulent rhinitis lasting several days. In the severe cases of mouth burns the most marked lesions were always on the hard and soft palate and the dorsum of the tongue. The mildest cases showed erythema of the same areas.

Respiratory Lesions as Seen at Autopsy

Case I, Private Ha.—

Nose.—Examination of anterior nares negative. No skin burns on nose.

Lips.—No burns of mucosa of lips.

Mouth and Neck Organs.—Tip of the tongue is negative. On the dorsum there are patches of grayish and grayish white coating beneath which the mucous membrane is desquamated. When the coating is removed there is a denuded reddened surface. These lesions increase in severity toward the root of the organ where they become diphtheritic in character and are covered with a greenish gray membrane. The tonsils and palatal arch show areas of diphtheritic necrosis covered with a grayish membrane. Mucosa of the palate is markedly edematous and presents elevated, reddened and grayish areas. The tonsils are about normal in size, with deep crypts. The right is negative on section. The left tonsil shows membranous patches and, on section, crypts containing fibrinous exudate. Mucosa of pharynx is covered with a thick, grayish, tenacious membrane, which, when pulled off, leaves a denuded, reddened surface. The epiglottis is covered with a thick, grayish mucus and the glottis

is filled with a similar mucus. Beneath this the mucosa is congested and shows small patches of superficial necrosis, but these lesions are less marked than in the pharynx. Below the glottis, the mucosa of the trachea is covered with a thick grayish mucus, beneath which the mucosa shows a congestion diminishing in intensity from above downward. There is no membrane in the trachea but in its lower portion and at the bifurcation there is a thick, grayish mucus in the lumen. The posterior wall of the trachea shows marked hypostasis but there is no visible necrosis of its mucosa. The esophagus shows congestion of its mucosa with superficial desquamation at the mouth but no changes below this.

Lungs.—There is no fluid in either pleural cavity. The lungs meet in the midline above the heart. Both lungs are free throughout. Pleural surfaces negative.

Left Lung.—There are delicate old adhesions between the upper and lower lobes. On the anterior surface of the lower lobe there is a small pigmented nodule beneath the pleura, a healed tubercle. There is no thickening or puckering of the pleura over the apex. Beneath the pleural surface there are numerous minute petechial hemorrhages which are larger and most abundant posteriorly. The lung is air-containing throughout. The upper lobe is voluminous and pink in color; the lower lobe shows marked hypostasis posteriorly. On section, the cut surface shows marked congestion and edema. Foamy fluid, thicker than the ordinary stasis edema, exudes abundantly from the cut surface. The lower lobe presents a marked hypostatic congestion. The small hemorrhages appear soft and fresh and the blood shows no discoloration. Small fresh agonal lardaceous clots are found in the larger pulmonary vessels, but no thrombi or emboli are visible to the naked eye. No pneumonic areas, no abscesses, no hemorrhagic infarctions and no airless areas are found. Anthracosis is moderate. The main bronchi are filled with a thick, frothy fluid which is rather viscous and is grayish white in color, but in the smaller branches becomes distinctly yellowish and thicker. Beneath this the mucosa of the bronchi is markedly congested.

Right Lung.—The right lung is very much heavier than the left and much deeper in color. There are delicate old adhesions between upper and middle, and middle and lower lobes. The lower lobe posteriorly is almost black in color, the middle lobe deep red, while the upper lobe is more pinkish. The subpleural hemorrhages are more marked in this lung than on the left side. The anterior margins of the lobes show emphysema. The greater part of the lower lobe shows a partial atelectasis and posteriorly a firm airless area almost black in color, about the size of a hen's egg. On section, there is extreme congestion and edema with areas of atelectasis throughout the lower lobe. Throughout the entire lung there are numerous firm, elevated, airless areas of small size, that are not wedge-shaped. The large airless area in the lower lobe is wedge-shaped with its base toward the surface, deep red, almost black in color and shows in its center a softer, lighter area, apparently around the blood vessel. No thrombi or emboli can be seen with the naked eye. The bronchi show the same fluid contents and changes in the mucosa as on the left.

Bronchial Nodes.—The bronchial nodes on both sides are rather small, soft, edematous and but slightly pigmented.

Microscopic Findings

Mouth.—Sections from the dorsum of the tongue show patches of diphtheritic necrosis and small ulcers from which the membrane has been loosened. The submucosa shows intense congestion, small-celled infiltration, some fibroblastic proliferation and numerous capillary thromboses. Some of the dilated vessels, either capillaries or lymphatics, are filled with coarse threads of fibrin without red blood cells and with only an occasional leucocyte. The mucous glands show intense mucoid degeneration with small-celled infiltration and many of the ducts are dilated and filled with mucus. Regeneration of the epithelium from the deepest portions of the folds and mouths of the mucous glands has begun. (See Fig. 20.)

Pharynx.—Sections of the pharyngeal wall show intact epithelium covered with a thick mucus. The submucosa shows marked congestion, edema and polynuclear infiltration with small areas of hemorrhage. There are numerous dilated capillaries or lymphatics filled with coarse threads of fibrin without red blood cells or leucocytes. The mucous glands show marked mucoid degeneration. The tonsils show marked congestion and edema. The greater part of the epithelium is intact, but there are localized patches of diphtheritic necrosis. There is an increase of the stroma and many sclerotic vessels.

Larynx.—Sections from larynx show a desquamative catarrhal laryngitis with small areas of diphtheritis (see Fig. 21). The epithelium is for the greater part necrotic, either entirely gone or represented by a single layer of nuclei. On the surface there is a thick mucofibrinous exudate forming a cast of the entire lumen and for the greater part separated from the necrotic surface. The submucosa shows congestion, edema and slight leucocyte infiltration.

Trachea.—The trachea presents the same condition as the larynx, a desquamative necrotic tracheitis with the formation of a thin mucofibrinous membrane over the surface.

Bronchi.—The larger bronchi are filled with a thick mucous exudate containing many desquamated cells, some polynuclear leucocytes and a few red blood cells, with little or no fibrin. The epithelium of the mucosa is in part intact, showing hydropic or mucoid degeneration, and in part desquamated. The bronchial walls show intense engorgement of the vessels, well marked edema and a moderate small-celled infiltration. The mucous glands show marked mucoid degeneration. The picture is that of a catarrhal desquamative bronchitis. (See Fig. 22.)

Lungs.—The lungs show extreme congestion and edema with numerous minute hemorrhages by diapedesis. Areas of emphysema and atelectasis alternate throughout the lung. The atelectatic areas show the most marked edema and are usually the areas in which hemorrhages are found. No pneumonic areas are found. The airless area in the lower right lobe is a recent hemorrhagic infarct, the central lighter portion being an artery obturated by a recent mixed thrombus. Other smaller recent hemorrhagic infarcts are found beneath

Fig. 20.—Case I, Private IIa. Mustard gas lesion of dorsum of tongue. Base of ulcer from which the diphtheritic membrane has become detached.

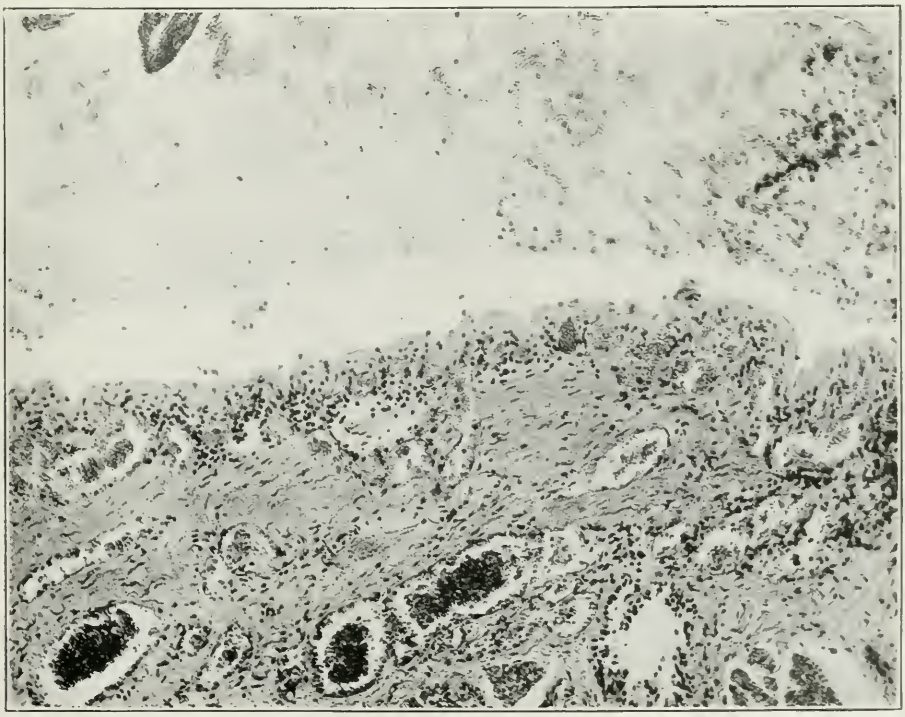

Fig. 21.—Case I, Private IIa. Section of diphtheritic lesion on vocal cord. Epithelium of mucosa completely destroyed and a mucofibrinous membrane partly detached from the surface. Extreme hyperemia of the vessels. Some small-celled infiltration.

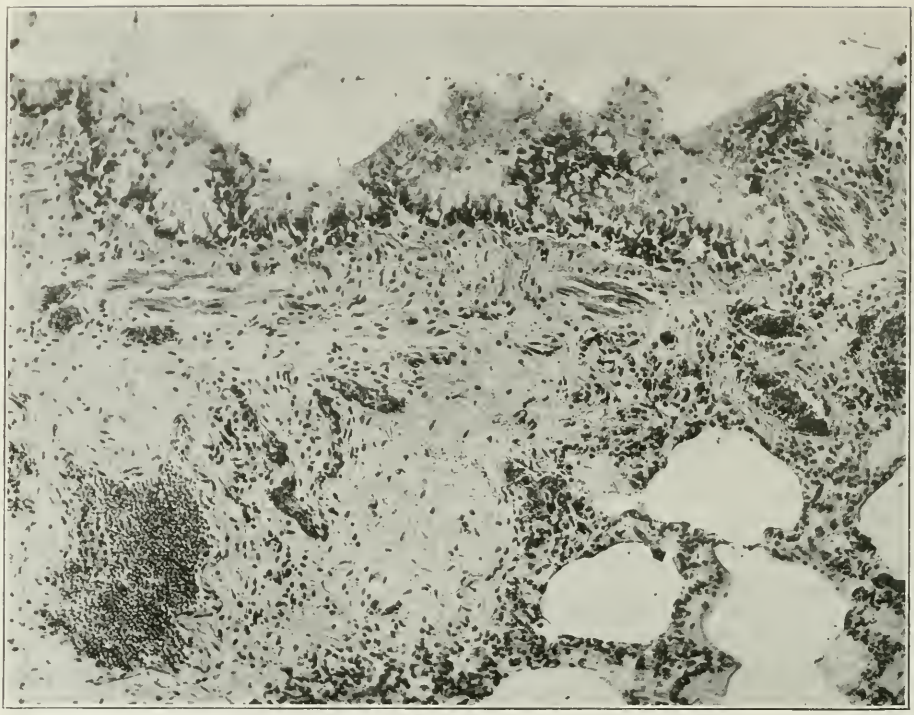

Fig. 22.—Case I, Private Ha. Section of main division of bronchus. Picture of catarrhal bronchitis. Marked mucoid degeneration and vacuolation of the bronchial epithelium. Congestion, small-celled infiltration, and edema of the bronchial wall.

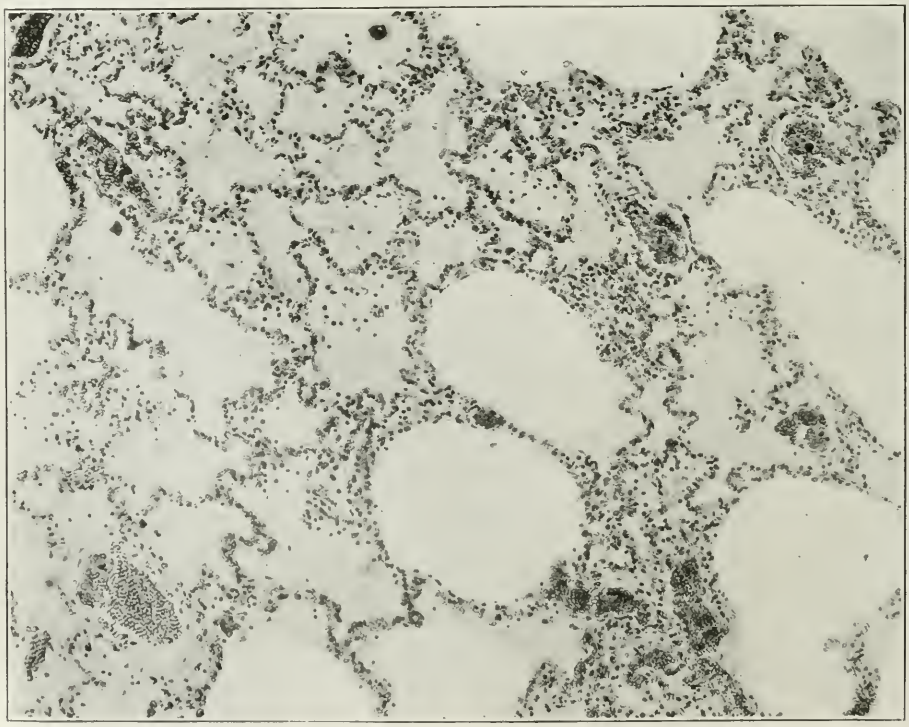

Fig. 23.—Case I, Private Ha. Section from upper lobe of lung. Congestion and edema. Acute emphysema.

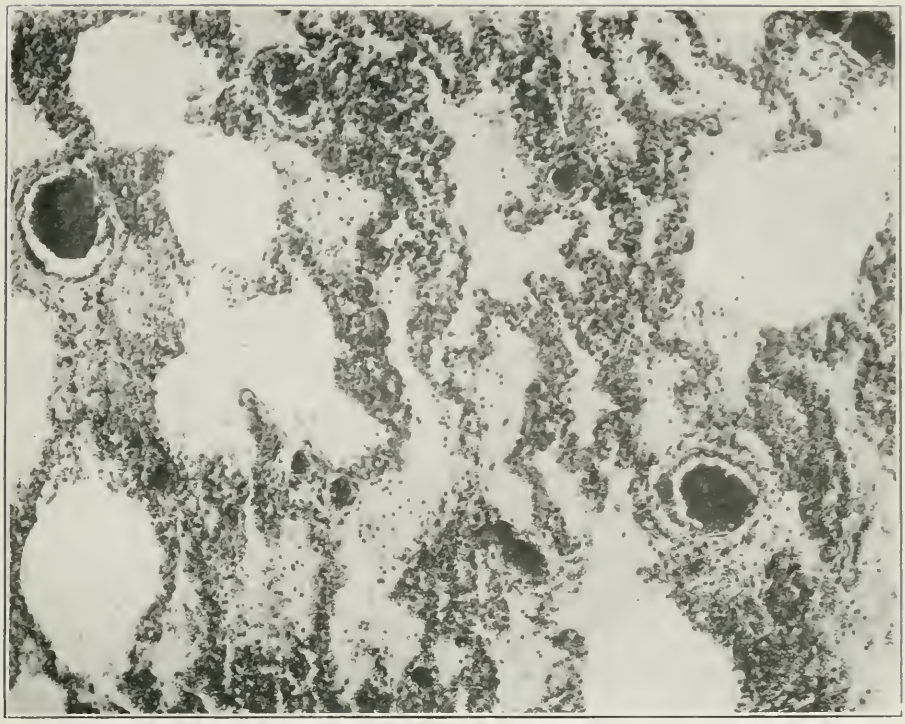

Fig. 24.—Case I, Private Ha. Section of lower lobe of lung. More intense congestion. Minute hemorrhages by diapedesis. Areas of partial atelectasis, alternating with emphysematous areas.

Fig. 25.—Case II, Private S. Mustard gas burns on lip, eight days after exposure.

the pleura of the right lung, with recent thrombi in the vessels leading to these areas. All the smaller bronchi and bronchioles are dilated and filled with a seromucoid fluid containing desquamated cells with some fibrin and occasional red cells. The epithelium of the smaller bronchi is intact for the greater part, but shows marked mucoid or hydropic degeneration. In many bronchioles desquamation of the epithelium has taken place. In no bronchi or bronchioles is there any purulent exudate. There are no old thrombi or emboli, and fat stains of frozen sections show no fat emboli. Smears of the bronchial exudate and from the cut surface of the lung show only occasional diplococci. (See Figs. 23 and 24.)

This case presents a marked degree of mustard gas degeneration and necrosis of the epithelium of the mouth cavity, larynx and trachea, decreasing in intensity to the larger bronchi and bronchial subdivisions, without infection or pneumonia. Death, in this case, probably resulted from shock and toxemia from the extensive areas of necrosed skin and secondary infection.

Summary of Clinical Observations

From the clinical cases coming under observation, mustard gas lesions of the respiratory tract in man are of the same nature as those produced experimentally in animals. In the milder cases there is an injury to the epithelium of the mucosa of the upper respiratory tract, particularly of the anterior nares, hard and soft palate, dorsum of tongue, pharynx, larynx and upper part of trachea. Rhinitis and laryngeal huskiness and cough with sore throat and thirst are the most common symptoms in individuals exposed to light and moderate concentrations. From these conditions recovery is usually prompt, but laryngeal huskiness and irritation may continue for some days or even weeks. No instances of secondary infection were observed in such cases.

In the more severe human cases, there is a greater degree of degeneration and necrosis of the epithelium of the respiratory tract, extending into the bronchi, but diminishing from the upper part of the trachea down, the most severe lesions being eschars on the palate, dorsum of tongue, pharynx and larynx. Associated with these, there is a widespread catarrhal tracheitis and bronchitis, with congestion and edema of the lungs. The one case autopsied showed no pneumonia. Under the conditions of warfare more severe exposures to mustard gas may produce diphtheritic lesions of larynx, trachea, and bronchi terminating in bronchopneumonia.

II. GASTROINTESTINAL LESIONS PRODUCED BY MUSTARD GAS

Practically no descriptions of gastrointestinal lesions produced by mustard gas exist in the literature. *Giraud* considered lesions of the digestive tract to be rare but thought that they might be caused by ingestion of food contaminated by the gas. In the clinical descriptions given in some of the army medical reports, as in the paper of *Mandel* and *Gibson* (*Journal American Medical*

Association, 1917, lxix, 1970-1971), epigastric distress, nausea and vomiting are frequent symptoms and appear in four to sixteen hours after gassing with mustard gas. *Pissarello* (*Giornale di Medicina Militare*, 1918, lxvii, 128-134) states that nausea and salivation are common symptoms in light cases and that vomiting, abdominal pain and diarrhea occur in the severe ones. These symptoms he considers reflex to the coughing. *Canelli* (*Rivista Ospedaliera*, 1918, viii, 2-6) gives the first published report of an autopsy on a case of mustard gas poisoning in which gastrointestinal lesions are described. He found the stomach distended with gas, the mucosa cloudy, glassy, congested in striæ, with numerous minute ulcerations along the major axis. Corresponding to the second flexure of colon there was a small, limited zone of subserous emphysema. The wall of the colon was thick, much congested and the mucosa was everywhere necrotic and covered with a sanious, purulent exudate. Corresponding to the second flexure of the sigmoid the necrosis extended into the submucosa and to the lowest strata of the wall. The duodenum showed a cloudy and congested mucosa, irregularly dotted with minute ulcers on a background similar to that of the stomach. The jejunum and ileum were nearly empty, anemic, semitransparent, with epithelium nearly uniformly desquamated. The esophagus and rectum showed no changes. In his macroscopic pathologic diagnosis, Canelli designates these conditions "acute gastroduodenitis with hemorrhagic erosions; acute desquamative enteritis, similar to the third stage of choleriform enteritis; severe diffuse hemorrhagic necrotic colitis." In his epicrisis he considers the acute inflammation of the colon to resemble macroscopically, in some particulars, both amebic and bacillary dysentery, although not clinically analogous, and considers that the gastrointestinal condition deserves special mention as indicating a selective action of yprite (mustard gas). He states further that in other reported necropsies upon cases dying from the action of other asphyxiating gases, without giving the references, chronic enteritis and gastrointestinal ulceration have been observed, and, therefore, concludes that there is a parallelism between the action of other toxic asphyxiative gases and mustard gas. *Karsner* noted in one autopsy case congestion of the stomach mucosa with submucous petechiæ in the fundus.

Other writers have hinted, without producing pathologic evidence, that the gastrointestinal symptoms are probably the result of mustard gas taken into the alimentary tract on contaminated food; but they may be due in many cases to shock or be secondary to the respiratory conditions.

EXPERIMENTAL

1. FEEDING.—Capsules containing .06-.24 c.c of dichlorethylsulphide were given to rabbits and guinea pigs in olive oil, butter and lard; similar capsules were given in meat to dogs. Animals were kept fasting, but were given water to drink. They were killed in series to get the complete pathologic picture from beginning to end of the process. For the purpose of brevity protocols are omitted, and the results of the experimental work are condensed as follows:

Symptoms.—These appear in 1-12 hours usually. Vomiting; irritation of

mucous membranes of mouth; profuse salivation; ultimately foul discharge from nose and mouth; foul diarrhea, at times tarry stools; depression; refusal of food and water. When allowed to live there is progressive anorexia, and weakness; by the sixth day the animals are so weak that they lie prostrate. Animal becomes greatly emaciated, with odor of foul putrefaction. Foul discharge from mouth persists. Death occurs usually by the 12th day, from .03-.06 c.c. doses, within three to five days from the .24 c.c. dose, for dogs, sooner for guinea pigs and rabbits.

Gross Pathology.—Delayed rigor mortis in animals not immediately autopsied. Emaciation. No free gas or fluid in peritoneal cavity. No general peritonitis. Liver congested; gall bladder dilated; spleen anemic, small and dry. Heart shows dilatation of right side. Peculiar chicken-fat clots in right ventricle of dogs. Lungs show varying degrees of congestion; no pneumonia. Kidneys congested. Chief lesions in gastrointestinal tract. Stomach and duodenum distended with gas and containing greenish or black fluid. Mucous membrane shows varying degrees of necrosis, localized in patches or extending over the entire surface. The necrosed areas appear greenish brown or gray, to black, without much inflammatory reaction. In the milder cases the mucosa may show marked congestion. Very little hemorrhage in stomach. Necrotic areas are usually thinned, but the animal usually dies before perforation occurs. Early peritonitis, over the thinned areas, occurs. Self-digestion by the stomach juices of the necrotic surface is delayed, from the inhibition of stomach secretions. Clean ulcers were not seen in the early cases, but were found in from six to twelve days, the ulcer extending into the muscle coat. The stomach lesions do not show the characteristic edema produced by dichlorethylsulphide in the skin and conjunctiva. A moderate edema was observed only in the cardiac end. The nonhemorrhagic character of the gastric lesions is also striking. Throughout the intestines there are patches of necrosis with congestion and slight hemorrhage, and more or less marked catarrh. Mesenteric glands swollen, edematous and congested. In the mouth, nose, pharynx, and esophagus of a certain proportion of the animals marked necrotic lesions, with secondary infection, occurred, as the result of local contact with the gas in swallowing or vomiting.

Microscopic Pathology.—Gastrointestinal mucosa shows varying stages and degrees of necrosis, involving the upper layers of the mucosa or extending through the submucosa into the muscle coats. In no case did the ulcer extend through the muscle. Preserved portions of the mucosa show dilated glands filled with granular or thready precipitate, or colloid masses, resembling hyaline casts. The epithelium of the deeper portions of the glands often shows a marked hydropic degeneration or liquefaction necrosis. There is usually little or no edema of the submucosa or tissues of the neighboring stomach wall. The eschar may be adherent to the surface, or the floor of the ulcer may consist of the muscle coats. These show polynuclear infiltration, congestion, some fibrinous exudate into the tissues, and occasionally hemorrhage. In the older cases there is often a marked small-celled infiltration of the muscle coats, extending to the subserosa, with fibroblastic proliferation of the latter and be-

Fig. 26.—Rabbit 44. Exposed twelve hours to a concentration of 1:50,000. Died ninety-two hours after gassing. Mustard gas eschar on tongue.

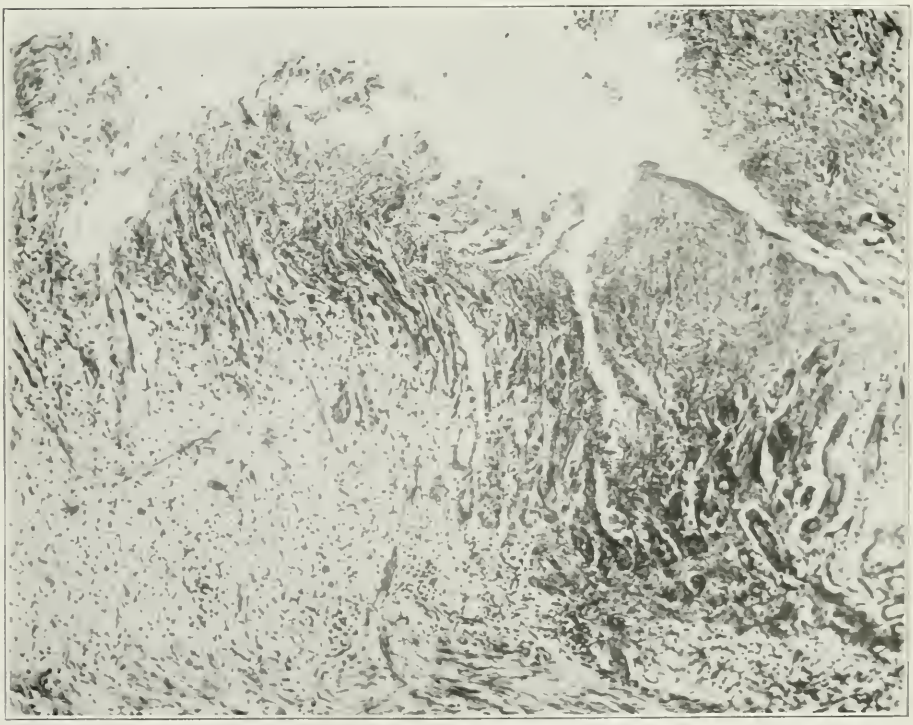

Fig. 27.—Dog 2. Received four minims of dichlorethylsulphide on meat. Died five days afterwards. Small mustard gas eschar in stomach mucosa. Early fibroblastic proliferation.

gimning peritonitis. The necrotic areas in the intestine are similar but show a more marked leucocyte infiltration, often extending to the serosa, but without any overlying peritonitis. The necrosis of the mucosa is most marked over the lymphoid tissue; Peyer's patches often being nearly completely necrosed. Numerous putrefactive bacteria are found in the necrotic areas of the mucosa. The entire mucosa is congested, and inflamed, showing occasional hemorrhages. The inflamed mucosa is but moderately edematous. There is marked mucoid degeneration of the epithelium. The mesentery is edematous, and shows at the insertion areas of inflammation. The mesenteric glands show sinus catarrh, and are congested. (See Figs. 27 and 28.)

2. Gastrointestinal Lesions in Gassed Animals.—In animals gassed

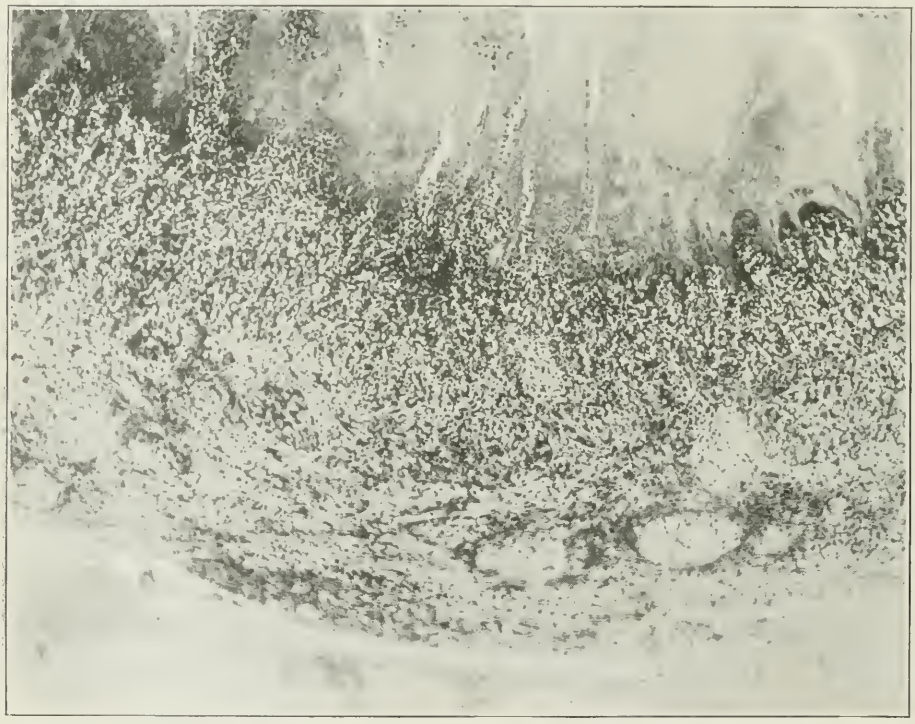

Fig. 28.—Dog 4. Received one minim of dichlorethylsulphide in capsule. Died twelve days later. Portion of base of very large eschar of stomach wall, extending nearly to the serosa. Marked leucocyte infiltration.

in the gassing chamber and not dying within several days there are found practically always a more or less severe congestion and catarrhal inflammation, which is more severe in the small intestine than in the stomach. In some cases, more severe lesions are found in the upper part of the digestive tract (diphtheritic necrosis, catarrhal inflammation, ulceration, etc.), but these can be explained as the result of gas swallowed with the air, saliva, or with food; and must be interpreted as direct local lesions. (See Fig. 26.) The generalized catarrhal condition of the small intestine may be explained by the assumption that dichlorethylsulphide or some substance resulting from it is excreted by the

intestine or through the bile or by the direct local action of minute quantities of mustard gas taken in with food or saliva and diffused throughout the gastrointestinal contents.

CLINICAL OBSERVATIONS

In the severe cases of mustard gassing seen by us, marked nausea and vomiting, gastrointestinal pain and diarrhea either preceded or were synchronous symptoms with the development of the cutaneous burns. We believe that these are reflex in nature and can be regarded as symptoms of the severe shock from which the patients suffered at this time. We also believe that the gastrointestinal symptoms seen in several patients after the symptoms of severe shock had disappeared were reflex and dependent upon the laryngotracheal-bronchial irritation (coughing).

In the fatal case the following gross appearances in the gastrointestinal tract were noted:

The *stomach* contains a small amount of thin, grayish fluid, slightly blood stained, and some milk curds. Throughout the entire mucosa there are numerous small petechial hemorrhages, these being most numerous toward the cardia where the mucosa is sprinkled with them, many of them being confluent. They all appear very fresh, the blood not being discolored and no erosions or ulcerations over them. The gastric mucosa is thin, smooth and soft, with early postmortem change. The *duodenum* contains a thin, grayish bile-stained fluid, the mucosa is congested and covered with a tenacious, thick, grayish mucus. Just below the pylorus there are numerous hemorrhages in the mucosa. The *small intestine* is distended with gas and at intervals there are small collections of thin fecal matter slightly bile stained. The mucosa is congested and there is marked hypostasis in portions of the loops without other changes. The *colon* contains gas and some formed fecal masses. The mucosa is negative.

Microscopic Findings.—The *stomach* shows a marked congestion of the vessels of the mucosa with numerous fresh hemorrhages. Postmortem digestion of the upper portion of the mucosa. The *duodenum* shows postmortem necrosis of the upper portion of the mucosa, congestion, and marked mucoid change in the glands of Brunner. The *small intestine* shows a postmortem desquamation of the surface epithelium, slight catarrh of the glands and congestion and edema of the mucosa. *Colon* shows a similar condition. *Appendix* shows evidences of old inflammation. No active process. The *mesenteric glands* show a marked sinus catarrh with many hemophages present in the sinuses.

It is hardly probable that the gastrointestinal changes observed in this case are the direct result of the mustard gassing. It is much more likely that they are entirely secondary phenomena.

(For the gastrointestinal lesions produced by subcutaneous and intravenous injections of mustard gas the reader is referred to the paper on "The General Pathology of Mustard Gas (Dichlorethylsulphide) Poisoning," *Journal of Laboratory and Clinical Medicine*, this number, p. 265).

CONCLUSIONS

I. RESPIRATORY TRACT

1. The action of dichlorethylsulphide mustard gas, upon the epithelium of the respiratory tract is escharotic in character, similar to its action upon the epidermis, cornea and conjunctival epithelium. Degeneration or complete necrosis of the epithelium, or deeper necroses extending into the submucosa, constitute the primary lesions produced in the respiratory tract by mustard gas in weak or strong concentrations. These lesions are most marked in the anterior nares, mouth, pharynx, larynx and upper part of trachea, diminishing in intensity toward the lungs. In the most severe cases, however, the bronchial epithelium may also undergo degeneration or necrosis. The subepithelial edema in the upper respiratory tract is not at all comparable in degree to that associated with mustard gas lesions of the skin and conjunctiva.

2. Following the primary lesion there develops a catarrhal or a diphtheritic rhinitis, localized stomatitis, pharyngitis, laryngitis, tracheitis or bronchitis.

3. In even the mildest cases there is marked congestion and edema of the lungs and catarrhal bronchitis. In the more severe cases the bronchitis may be diphtheritic in character. Secondary infection may occur, and, following the development of a purulent bronchitis, a purulent bronchopneumonia may result. We have observed no pneumonia resulting directly from the gassing. All of the pneumonias observed, following the gassing, have been the result of secondary infection.

II. GASTROINTESTINAL TRACT

1. Direct application of mustard gas to the mucosa of stomach or intestine, by means of contaminated food, produces localized degeneration, necrosis and ulceration similar in type to the lesions of the respiratory tract.

2. The mild catarrhal conditions and small localized eschars of the stomach and upper portion of the small intestine seen in animals gassed in the gassing chamber may be explained as the result of minute quantities of mustard gas swallowed with air or dissolved in the saliva.

3. The gastrointestinal symptoms seen in gassed human beings are probably chiefly reflex, either associated with shock or with the respiratory irritation. As in other forms of gassing, it is probable that erosions or ulcers of the stomach and intestine may be embolic in character, the emboli arising in the primary or infected mustard gas lesions of the skin or elsewhere. It is also possible that in man, as in the case of animals, localized eschars of the gastrointestinal mucosa may be produced by the direct action of mustard gas swallowed in contaminated food or saliva.

THE GENERAL PATHOLOGY OF MUSTARD GAS (DICHLORETHYL-SULPHIDE) POISONING*

By Aldred Scott Warthin, Ph.D., M.D., and Carl Vernon Weller, M.S., M.D., Ann Arbor, Mich.

VICTOR MEYER, the discoverer of dichlorethylsulphide, believed that mustard gas applied to the unbroken as well as to the scraped skin of rabbits could produce lesions in other parts not directly touched by the application (eyes and auditory canal). He also made a subcutaneous injection of two drops into the back of a rabbit. No effects were noted at the site of the injection, but the animal developed inflammation of both eyes, with severe snuffles, and died of pneumonia on the third day. From these data he concluded that the most severe action of dichlorethylsulphide develops only after its entrance into the blood. *Haldane* is reported as having confirmed Meyer's observation, by producing conjunctivitis and death from pneumonia through injection. *Kolls and Gilbert* have observed that 10 mg. of an alcoholic solution injected into the muscles and also intravenously caused only a temporary depression and loss of appetite with recovery in a week; but similar injections of 50-100 mg. in alcohol and water emulsion produced convulsions within one hour, and death in three hours.

The general trend of the clinical observations made by French and Italian medical men in field hospitals is to the effect that the lesions of mustard gas poisoning are local, and that no general toxic action is produced. *Giraud* makes the definite statement that all of the lesions observed by him were purely local. He only rarely saw general symptoms, rapid pulse and fever; and these symptoms he thought might be due to other causes than an intoxication. The frequent vomiting he considered dependent upon the respiratory irritation and attempts at coughing. *Mandel and Gibson* do not speak of any general toxic symptoms. *Pissarello* also considered the frequently occurring vomiting to be reflex to coughing. He concluded that ocular symptoms are due entirely to the direct action of mustard gas vapor; and that they are not produced by any substance in the blood of the gassed; and, further, carried out a series of experiments to show that there was no poisonous substance irritant to the conjunctivæ in the tears or sweat of soldiers suffering from mustard gas conjunctivitis. Since gastric symptoms, hemorrhage and ulceration, have been noted in other forms of gassing, notably with chlorine, some writers have assumed their analogous occurrence in mustard gas poisoning.

Canelli, in the first published Italian autopsy protocol of a mustard gas death, notes, in addition to the local lesions of skin and respiratory tract, a parenchymatous degeneration of the liver, fatty cloudy swelling of the kidneys, hemorrhage into adrenal medulla, acute gastroduodenalitis with hemorrhagic erosion, an acute desquamative enteritis, and severe diffuse hemorrhagic necrotic

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colitis. He seems inclined to the belief that the gastrointestinal lesions are analogous to those produced by other forms of gassing. *Mackenzie* in autopsies upon animals gassed with dichlorethylsulphide observed focal necroses in the liver, punctate hemorrhages in adrenal cortex, swelling and hyperemia of the gastroduodenal mucosa, and in one case hemorrhagic ulcerations near the pylorus. He could not, however, ascribe any positive relationship of these findings to the gassing. *McNee* observed acute hemorrhagic nephritis, degenerative changes in the central portion of liver lobules and minute hemorrhages in the brain, in a few instances. In the four mustard gas autopsies reported by *Karsner* the only pathologic findings, aside from the local lesions of skin and respiratory tract, were a dusky red congestion of all the viscera, including the brain in two cases, and submucous petechiæ in the fundus of the stomach.

The question of the internal pathology of gassing with mustard gas is, therefore, not yet satisfactorily answered; and the object of the investigations recorded in this paper has been to throw some light upon this problem.

I. GENERAL PATHOLOGY OF ANIMALS GIVEN LOCAL APPLICATIONS OF DICHLORETHYLSULPHIDE TO SKIN OR CONJUNCTIVA, OR EXPOSED TO ITS VAPOR IN GASSING CHAMBER

From observations made upon a large number of animals exposed to mustard gas, either by direct applications to the skin or eyes, or in the gassing chamber, the systemic symptoms shown consist of gastrointestinal disturbances, such as vomiting and diarrhea; disturbance of heart rate, usually an increased rate, but in severe cases the rate may be slowed; lowering of the temperature except with infection; decreased urinary elimination; in the blood a secondary anemia, leucocytosis or leucopenia; and nervous symptoms, as increased reflex excitability, tremors and convulsions, or marked depression, stupor and coma. The great majority of slightly or moderately gassed animals show no systemic phenomena. The most constant of the general symptoms are the gastrointestinal. While a certain number of cases showing these symptoms may be explained as resulting from slight quantities of mustard gas swallowed in the air or saliva, or on food particles, it is probable that the gastrointestinal symptoms are chiefly reflex to the respiratory irritation, or are a part of the general phenomena of shock. In all severe dichlorethylsulphide gassing an initial shock is very common, and the changes in temperature, circulation, etc., form part of the clinical picture of this condition. With the development of pneumonia or localized infection the usual systemic symptoms attending such processes are observable.

We have seen nothing to make us believe that Victor Meyer's idea, that the toxic action of mustard gas is exerted chiefly through the blood, is correct; indeed, all of our observations make us certain that local applications of mustard gas to the skin of distant parts can not produce conjunctivitis or local lesions at other sites. Meyer's conclusion was based upon an error in technic.

The insidious character of mustard gas, the difficulty in handling it, the ease by which invisible droplets, spray or vapor may be conveyed, and the frequent occurrence of such secondary transmitted lesions explainable in this way, are sufficient grounds in explanation of Meyer's incorrect judgment.

Likewise the pathologic findings in gassed animals give no convincing evidence of the absorption of mustard gas into the blood from the skin, eyes, or respiratory tract. The general pathology is as follows:

Central Nervous System.—Congestion; very rarely minute hemorrhages; in infected cases emboli are seen rarely.

Thyroid.—Congestion; no other changes, except as involved directly from the laryngeal lesions. This event is common enough in the severe cases of laryngeal and tracheal diphtheritis, when the thyroid is congested, edematous and infiltrated with leucocytes.

Heart.—Ventricles usually dilated. No changes observable in heart muscle.

Aorta.—Intima of great vessels occasionally shows fatty streaks.

Lung.—When not involved directly through the respiratory tract, as in local application to the skin, the lung shows congestion, with or without edema. In the case of infected skin or eye lesions pulmonary emboli, metastatic pneumonia, etc., may occur.

Spleen.—Congested. In some cases an increase in the number of pigmented phagocytes.

Adrenals.—Congestion. Occasionally minute hemorrhages in medulla. (These are probably postmortem.)

Kidneys.—Congestion. Frequently slight cloudy swelling. In infected cases more marked cloudy swelling, casts.

Pancreas.—Congestion.

Liver.—Marked congestion. In the majority of cases liver cells are normal; slight cloudy swelling and fatty changes are not rare, but their occurrence does not suggest any direct relationship with the gassing.

Gall Bladder.—A thinner, watery bile is usually present.

Gastrointestinal Tract.—Congestion and mucous catarrh are always present. Minute hemorrhages and erosions are frequently seen in stomach (vomiting?). Very rarely embolic hemorrhages and erosions occur, especially in animals with large eschars, or infected lesions. At times local eschars of the gastric mucosa occur; these are explainable as due to ingestion of contaminated food or saliva. The marked salivation seen in many animals and the swallowing of quantities of such saliva containing small amounts of mustard gas, offer a plausible explanation for the catarrhal conditions found in the gastrointestinal tract, without assuming, as some writers have done, that they are due to an excretion of mustard gas through the gastrointestinal mucosa. The intense splanchnic congestion usually present may also serve to explain the gastrointestinal conditions.

Mesenteric Lymph Nodes.—Congestion and edema.

Genital Organs.—No changes noted.

Urinary Bladder.—Negative.

II. GENERAL PATHOLOGY AS SHOWN IN HUMAN AUTOPSY

The protocol of the gross and microscopic general pathology of the one human autopsy case of fatal poisoning from mustard gas seen by us is given here in full, with the exception of the respiratory and gastrointestinal tracts, which are given in the preceding article.

AUTOPSY PROTOCOL.—*Private Ha.* Died 12:30 P.M., July 8, 1918.

(Autopsy by Dr. A. S. Warthin, 2:00 P.M., July 8, 1918.)

External Examination.—Young adult male body, length 170 cm., strong build, frame large, thorax deep, epigastric angle a right angle, abdomen on level with ribs. Musculature good, well developed. Panniculus abundant, particularly over abdomen and thighs. Hips rounded, slightly of feminine type. Neck thick, thyroid small, facies slightly suggestive of mouth breathing; general appearances of body suggest the lymphatic constitution. All regional lymph nodes prominent. Hair of head abundant, dull brownish in color, dry; scalp shows much dandruff. Face shaven, beard not heavy, body hair fairly abundant, pubic hair of feminine type. External genitals small, scrotum small, tight; testicles small; penis medium size, moderate phimosis. No anomalies. No deformities, defects or mutilations. No surgical wounds or scars.

Hypostasis.—Moderate postmortem hypostasis, pale in color, except over hyperemic areas. Superficial veins on upper portion of body contain but little blood.

Rigor Mortis.—Marked rigor mortis throughout body, except in right arm, where it has been broken by manipulation of the arm.

Body Heat.—Body is cold. (Cooled by undertaker.)

Odor.—Marked odor of gangrene over the skin, particularly from that of back.

Skin.—Marked pigmentation of skin of face, hands and forearms. Right hand shows irregular patches of pigmentation alternating with paler recent scars of older (mustard gas) burns. Hands show irregular patches, particularly between the fingers, of desquamation of the horny layer. No recent burns on hands.

Over the greater part of the body, from the collar line down to the boot line, the skin presents the appearance of a chemical burn, varying in degree from hyperemia, slight desquamation, dried blebs and bullæ, denuded areas, to areas of well-marked necrosis and eschar formation. These lesions are most severe in the axillary regions, inner aspect of arms, bends of elbows, flanks, genitals, thighs and back. Severe lesions completely encircle both thighs, particularly marked posteriorly where there is extreme necrosis, secondary infection and pus formation. The necrosis is very marked over the entire back, neck, shoulders and buttocks, where the skin is discolored, mottled red, grayish, yellowish gray, brown, black or greenish, with marked gangrenous odor. Deeper points of hyperemia corresponding to the hair follicles show in these discolored areas. Over a large part of these lesions the epidermis is desquamated in large bullæ, and the desquamated surface is brown, yellow or red. There are no large hemorrhages into these lesions, and very few petechial hemorrhages, the reddened areas being hyperemic only, the redness disappearing on pressure. From the discolored moist areas a cloudy foul-smelling serum exudes. This is not blood stained in any region. Through the hyperemic areas in many regions the hair follicles appear as opaque, yellowish miliary nodules. These are particularly marked over the scrotum.

The skin of the abdomen is hyperemic with a pale belted line corresponding to the protection afforded by belt worn by patient. This belted area of less injury disappears in the flanks and shows but slightly on the back. The anterior surfaces of the thighs are bright scarlet, marked hyperemia. The hyperemia stops rather abruptly over the legs about 15 cm. below the lower border of the patella. The lower portions of the legs show practically no involvement anteriorly; posteriorly there is slight discoloration and hyperemia (hypostasis?). The feet show no lesions.

The *face* shows no lesions except on the right side, around and below the right ear, where there is a slight desquamation of the epidermis, with some reddening of the edges and elevated portions of the lobe of the ear. Below the left ear there is slight desquamation without reddening. Over the *neck,* below the chin, are patches of dried vesicles, brownish red where the epidermis is desquamated, and red where it is still intact. The

hair shows no changes. On the *scalp* the only lesion found is an area of hyperemia above the right mastoid prominence. Here the scalp is scaly with a large amount of dandruff.

It is notable that the skin over the bony prominences, particularly over clavicles, scapulæ, etc., shows circumscribed patches of deeper eschar formation.

The areolæ of both nipples show strikingly the greater intensity of the injury around the hair follicles and sebaceous glands. Each nipple is surrounded by a deep zone of hyperemia in which the epidermis has been lost; through the hyperemic skin the yellowish, enlarged hair follicles can be seen.

The skin of *penis* and *scrotum* is discolored, necrotic and gives off a foul gangrenous odor. There is a well-marked phimosis, but the small portion of the glans exposed, around the meatus, is necrotic, yellowish and infiltrated with pus. A drop of pus exudes from the meatus. The remaining portion of the mucosa of the glans shows a marked inflammatory reaction (hyperemia, infiltration and edema). Through the discolored skin of the *scrotum* the yellowish necrotic enlarged hair follicles and sebaceous glands stand out prominently. Around the anus there is a zone of marked gangrene and suppuration of the skin.

The areas of skin (face, hands, legs and feet) not affected by the lesions show marked anemia.

Mucous Membranes.—These are pale, particularly the lips. They are dry but show no burns. Tip of the tongue shows no lesions. (See below.)

Eyes.—The cornea and conjunctivæ of both eyes are clear; there is no hyperemia, no discharge, no opacity. No signs at all of conjunctival involvement.

Nose.—Nasal openings negative.

Ears.—Auditory passages negative.

Edema.—Trace only about ankles; none in eyelids or below eyes. Over the burned areas the skin is swollen, tumefied, infiltrated, consistency increased, but pits only slightly on pressure.

MAIN SECTION

On section the panniculus is abundant, pale yellow, moist shining, and only slightly edematous. The superficial veins are markedly anemic. No free gas in *peritoneal cavity*. Abdominal recti deep red in color, with lighter patches of hyaline or Zenker's necrosis (as in typhoid). *Omentum* lies a handbreadth below the umbilicus, is very rich in fat; its vessels are empty.

There is no free fluid in the cavity. The *peritoneal surface* is clear, shining, rather dry, but shows no signs of inflammation. Upper coils of *small intestine* are distended with gas. *Cecum* is greatly distended, also *transverse colon*, and *descending colon* as far as the sigmoid.

Hepatic and *splenic* flexures collapsed.

Stomach in normal position, contains a small amount of fluid and gas. Vessels of stomach enormously congested. Pylorus is in normal position. Old adhesions around the *appendix*, but no active process. The appendix is 10 cm. long, patent throughout, and empty.

Lower border of *liver* in median line is three fingerbreadths below the ensiform, and about one fingerbreadth below costal margin in the right nipple line. The *spleen* is in normal position, the lower pole about two fingers above the costal margin.

The *diaphragm* on the left is in the 5th i.c.s., and at the 5th rib on the right.

The *thoracic muscles* are deep red, very dry and anemic.

The *costal cartilages* are white, and cut easily.

No free gas or air in the *pleural cavities*.

The *sternum* shows normal consistence, and its red marrow is in normal amount and appearance.

The *anterior mediastinal fat* is very abundant and shows numerous petechial hemorrhages. The fat is very abundant over the *pericardial sac*, and shows numerous petechial hemorrhages.

The *thymic fat* is abundant and contains numerous petechial hemorrhages. In it, the *thymus* is still present in the form of two distinct lobes, each of which is 5 cm. long and 3-5 mm. thick. Its color is pink, consistence firm; no hemorrhages in its substance.

The *lungs* meet in the middle line above the heart. The *apex* of the heart is in the 5th i.c.s., inside the left nipple line.

Both *lungs* are free throughout. There is no fluid in either pleural cavity.

Pericardium.—No gas in pericardial sac; fluid normal in amount, clear amber. Pericardial lining smooth, clear, moist, shining.

Heart.—Heart is small, smaller than cadaver's right fist; in marked rigor mortis, the left ventricle completely contracted, and the right one nearly so. The *auricles* and *venæ cavæ* are collapsed, nearly empty; on section contain but a small amount of dark fluid blood. The subepicardial fat is in excess; over the pulmonary artery, just above the conus, is a sclerotic patch ("soldier's spot") about the size of a dime; along the coronary branches, posteriorly over the left ventricle, are narrow stripes of sclerosis. There are numerous subepicardial hemorrhages, most marked in the neighborhood of the auriculoventricular groove. On section the heart contains a very little fluid blood and small thin lardaceous agonal clots, particularly in the right ventricle, extending into the pulmonary artery.

The *mitral* opening admits two fingers; the flaps are negative. In the left auricle a small agonal lardaceous clot. The left ventricle wall measures 20 mm. in thickness, the *muscle* is deep brownish red, firm, and shows no cloudiness, fibroid patches or fatty change. No fatty change seen beneath the endocardium.

The *tricuspid* opening admits three fingers barely. Its flaps are normal. Small agonal clot in right auricle. The *foramen ovale* is patent, an oval slit admitting probe 3 mm. in diameter, but well guarded by membranous curtain. The *pulmonary artery* admits two fingers, the pulmonary semilunar valves are negative. The *right ventricle* wall measures 3-8 mm. in thickness, about one-half of this being fat tissue. The *aortic opening* admits the thumb easily. Its semilunar flaps negative. The beginning of the aorta shows very fine stripes and patches of fatty degeneration of the intima. Arch of aorta negative; also its main branches. Pulmonary artery and main branches empty and negative.

(For protocol of lungs, see paper on Respiratory Lesions.)

Examination of *thoracic duct* negative.

Thoracic aorta shows linear stripes of fatty degeneration.

(For protocol of mouth and neck organs, see paper on Respiratory Lesions.)

The cervical *esophagus* shows some injection of its mucosa at its mouth with superficial desquamation; below this no changes except postmortem hypostasis. A small amount of stomach contents in the lower portion.

The *thyroid* is small; but on section shows normal amount of colloid.

Parathyroids, four in number, brownish in color, about normal size.

Cervical nodes are about normal in size, some larger, translucent, slightly edematous.

Parotid and submaxillary glands are normal in size and appearances.

Great vessels and nerves of neck region are negative.

Abdominal Organs.—The *spleen* is somewhat enlarged, soft, flattens on the board, its capsule slightly wrinkled. On its surface are the remains of a few old adhesions to the diaphragm. On section the pulp is soft, deep brownish red, rises above the trabeculæ, the cut surface slightly shagreened. Bleeds rather poorly. Follicles barely visible. There are no infarcts, abscesses, or other lesions apparent.

The *adrenals* are surrounded by abundant fat tissue. Both are normal in proportion, the cortex pale yellow and somewhat fatty, the medullary portions showing no postmortem changes. No pathologic changes apparent.

The *kidneys* have large fatty capsules. Fibrous capsules strip very easily. Both kidneys somewhat enlarged, plump and markedly congested. Surfaces smooth, veins congested. On section both kidneys bleed freely. The cut surface shows extreme congestion; the outlines between labyrinths and medullary rays are not distinct. The surface is slightly cloudy (slight or moderate cloudy swelling). The pelvis of the left kidney is negative; that of the right is dilated, filled with cloudy urine, and its mucosa slightly injected.

The left *ureter* is normal in size and appearances; the right is dilated with cloudy urine.

The *urinary bladder* is moderately distended, containing about 60 to 70 c.c. of turbid urine. Mucosa is pale, negative.

The *prostate* is of normal size and shape; on section normal in appearance.

The *seminal vesicles* contain a small amount of thin brownish semen on the right side; on the left they are nearly empty; and the walls show some thickening.

The *testes* show congested tunics. No fluid in sacs. On section both organs are rather small, slightly congested and slightly edematous. The left testis shows slight fibrosis extending from the rete.

(For protocol on gastrointestinal lesions, see preceding article.)

The *liver* is much enlarged, particularly the right lobe; but the lower border is rather sharp. Capsule negative. Surface smooth. Color deep brownish red with paler anemic

areas. On section bleeds very freely. Consistency fairly firm. Cut surface uniform deep reddish brown, the lobules enlarged, with congested central areas and slightly cloudy parenchyma (slight cloudy swelling). Anemic areas show slight fatty shine.

The *bile passages* are patent. Gall bladder small, contains a moderate amount of thick brownish bile, no concretions.

The *portal vein, common duct* and *inferior vena cava* negative on section.

The entire *splanchnic area* is congested.

The *retroperitoneal* and *mesenteric* lymph nodes are enlarged, markedly congested and somewhat edematous. The prevertebral *hemolymph nodes* are hyperplastic, deep red, and very numerous.

The *thoracic* and *abdominal aorta* small in size (hypoplastic), empty; the intima shows linear stripes of fatty degeneration, most marked in the neighborhood of the coeliac axis.

Semilunar ganglia and *solar plexus* negative.

Nervous System.—*Head.*—The *scalp* is negative except for changes mentioned above. Periosteum of cranium negative. In the right parietal bone a circular area of slight hyperostosis resulting from a cephalhematoma at birth. Corresponding to this area of elevation, there is on the inner surface of the *skull cap* a marked pacchionian depression almost perforating the greatly thinned outer table. The skull cap is thin; dura adherent all over; the meningeal grooves and pacchionian depressions unusually marked for age of cadaver; the lamina vitrea rough and dull; the dura is thickened throughout. The arachnoid shows numerous focal thickenings; the subarachnoidal fluid is markedly increased (edema); no evidences of inflammation. *Central longitudinal sinus* is negative. The *basal meninges* are slightly thickened and unusually tough.

The *basal vessels* are negative.

The entire *leptomeninges* are somewhat thickened, but strip easily.

The *cerebral convolutions* are rather sharp, but show no focal lesions. The ventricles are somewhat dilated; the cerebrospinal fluid is increased greatly, but is clear. The *ependyma* is normal.

The *choroid plexus* is markedly congested on both sides. The *pineal* gland is normal in size and appearance. On section the *cerebrum* shows congestion and edema. No hemorrhages found.

The *cerebellum* shows marked congestion and edema. Dentate nuclei are normal. No lesions in cerebellar lobes. The *basal ganglia, internal* and *external capsules* are negative.

The *pons* and *medulla* are congested and edematous. No lesions apparent.

The *cervical cord* shows slight congestion and edema. No lesions seen.

The *hypophysis* is of normal size, congested.

Basal sinuses congested. Base of skull negative.

Provisional Gross Pathologic Diagnosis.—"Mustard gas" burns of skin and upper respiratory tract; gangrene and secondary infection of skin; shock; toxemia; edema, congestion and early hemorrhagic bronchopneumonia. Passive congestion of all organs. Splanchnic congestion marked. Moderate parenchymatous degeneration of kidneys and liver (toxic); multiple petechial hemorrhages; congestion and edema of brain and cord; thymicolymphatic constitution.

MICROSCOPIC FINDINGS

Cerebrum.—Sections taken from all parts of the cerebral cortex, basal ganglia, floor of ventricles, internal capsule, show intense congestion, edema and a few minute perivascular hemorrhages.

Pons, Medulla and *Cerebellum.*—Show a similar congestion and edema.

Meninges.—Old thickenings. No active process. Marked congestion of the vessels and edema. In the larger pial veins there are agonal clots rich in leucocytes.

Hypophysis.—Intense congestion, otherwise negative.

Pineal Gland.—Large calcareous concretion. Gland substance smaller in amount than normal. Marked edema.

Spinal Cord.—Edema. Congestion. Postmortem myelinosis.

Heart.—Subepicardial fat abundant. Vessels congested. Numerous petechial hemorrhages throughout the fat. Heart muscle fibers somewhat smaller than normal—an acute simple atrophy. Stroma somewhat increased around the coronaries in the left ventricle wall. Endocardium is negative. Heart muscle shows very slight parenchymatous degeneration. No fat. Mixed agonal clots taken from the heart show white clot with very few leucocytes while in the red portions of the clot there are large collections of leucocytes.

Aorta.—Stripes of marked fatty degeneration in the intima. These are longitudinal

and stain rather brownish red with sudan III and also a brownish red with scharlach R. Osmic acid not successful.

(For respiratory tract and neck organs, see preceding article.)

Thyroid.—Vessels congested. Otherwise negative.

Cervical Lymph Nodes.—Show marked sinus catarrh with numerous hemophages in the sinuses. The *cervical hemolymph nodes* show marked congestion and hemolysis, many hemophages in the sinuses.

Thymus.—Remains of thymus scattered throughout the thymic fat with large corpuscles of Hassall, many of which are calcified.

Spleen.—Marked acute passive congestion. Small hemorrhages scattered throughout the pulp. Acute lymphoid exhaustion. Follicles very small with central exhaustion and degeneration. No degeneration of the central portion of the follicles seen as in burns of the skin. No thrombi, no emboli or infarcts.

Adrenals.—Slight cloudy swelling of the cortex. No increase in fat content. Congestion. Edema. Chromaffinic substance small in amount.

Kidneys.—Intense congestion. Cloudy swelling, particularly of the convoluted tubules. Numerous small precipitates of phosphates in the straight tubules of the cortex (concentrated urine). Marked edema of the connective tissue around the larger vessels and of the medullary portion. Very few casts. Frozen sections show no fat.

Bladder.—Congestion and edema. Otherwise negative.

Prostate.—Congestion. Gland spaces filled with secretion and desquamated epithelium. No pathologic changes. The prostatic plexus contains an organizing thrombus.

Seminal Vesicles.—Negative. The one apparently hyaline, shows only collapse of the wall; empty but no fibrosis.

Posterior Urethra.—Negative.

Testes.—Very little normal spermatogenesis. Many atypical division figures and desquamation of spermatids. Stroma is increased throughout, basement membrane thickened. Appearances suggest an old mumps orchitis. Intense congestion of the vessels.

Epididymes.—Negative.

Penis.—Foreskin edematous. Vessels congested, with areas of complete necrosis of the epithelium and of the subepithelial tissues. Where the epidermis is intact the horny layer is thickened and the epithelium beneath shows evidences of regeneration. The glans shows likewise areas of necrotic epithelium with areas of regeneration and other patches in which the horny layer is greatly thickened and adherent. The meatus shows a slight inflammation. The body of the penis shows areas of regenerating epithelium covered with a dense desquamated horny layer. Large areas of the surface are denuded, the epithelium necrotic, the necrosis extending into the subepithelial tissues. Marked congestion and edema throughout the organ and a mild diffuse inflammation.

Liver.—Acute passive congestion. Slight cloudy swelling. Fat stains show no fatty degeneration but a few scattered cells containing large droplets of fat.

Pancreas.—Congestion. Early postmortem softening. No other pathologic changes. Islands numerous, many of them very large.

Stomach.—Postmortem digestion of upper part of mucosa. Congestion. Hemorrhages.

Duodenum.—Postmortem necrosis of mucosa. Marked mucoid change in glands of Brunner.

Small Intestine.—Postmortem desquamation of epithelium. Congestion. Edema. Slight catarrh.

Colon.—Similar changes.

Appendix.—Evidences of old inflammation. No active process.

Mesenteric Glands.—Lymphoid hyperplasia, with exhaustion of the germ centers. Marked sinus catarrh. Many hemophages.

Retroperitoneal Hemolymph Nodes.—Marked congestion of sinuses. Great numbers of hemophages.

Skin.—The skin taken from various portions of the body shows complete necrosis of the epidermis and greater part of the corium reaching as far as the sweat glands over the greater part of the surface, but in many instances reaching the subcutaneous tissues. Many colonies of bacteria are found upon the necrotic corium but there is very little leucocytic infiltration in the necrotic corium or at the border between the living and dead tissues. Only in scattered areas where there is evidently a localized secondary infection are there any notable collections of polynuclears. The vessels in the lower portion of the corium show intense congestion, stasis. In the lymphatics there is a heavy albuminous precipitate with coarse fibrin threads. The lower border of the corium and upper portion

of the subcutaneous fat shows usually a well-marked edema. No old thrombi are found and very few hemorrhages, only here and there have a few red blood cells escaped from the vessels. More recent clots with heavy threads of fibrin are found in many of the distended vessels. In these clots many hemolyzed red blood cells are seen. Some hyaline clots are found in the areas of marked necrosis and secondary infection, but these may be secondary to the latter process. Fibroblastic proliferation has begun at the lower border of the necrotic corium and is particularly marked around many of the blood vessels and sweat glands. Regeneration of epithelium from the hair follicles and sweat glands has begun in many areas and in some instances extends to the surface. Separation of the eschar has begun in some areas. Every degree of change is shown from areas where the necrotic epithelium is still adherent, to those areas where the slough is beginning to separate, and to areas of beginning regeneration. A striking feature of the process is that the sebaceous glands are everywhere completely necrosed, but islands of regenerating squamous epithelium mark the site of these glands. The sweat glands also show marked degeneration, the majority of the acini being necrotic or hydropic. Regeneration of epithelium occurs almost entirely from the hair follicles and ducts of the sweat glands. Around the nipple, in the axillary region and over the scrotum the necrosis is deeper and more marked and the large sweat glands of the axilla show marked degeneration. In the scrotum the necrosis extends deep into the dartos involving the superficial bundles of involuntary muscle. In the scrotum, also, regeneration of epithelium proceeds from the hair follicles.

Final Pathologic Diagnosis.—Mustard gas burns of skin and upper respiratory tract. Necrosis, secondary infection and gangrene of skin. Acute necrotic pharyngitis. Acute catarrhal laryngitis, tracheitis and bronchitis. Congestion and edema of lungs. Multiple hemorrhagic infarctions of lungs. Acute passive congestion of all organs. Multiple petechial hemorrhages. Marked fatty degeneration of intima of aorta. Parenchymatous degeneration of kidneys and liver. Splanchnic congestion. Shock. Toxemia. Secondary anemia. Hypoplasia of heart and aorta. Thymicolymphatic constitution. Hyperplasia of hemolymph nodes with excessive hemolysis. Organizing thrombus in prostatic plexus. Old orchitis (mumps?).

SUMMARY OF CASE

The pathological findings in this autopsy case give no evidence of a systemic action of dichlorethylsulphide. All of the changes seen can be explained as due to the direct local action of the mustard gas vapor, or as secondary to the shock and secondary infection of the lesions.

III. GENERAL PATHOLOGY RESULTING FROM SUBCUTANEOUS AND INTRAVENOUS INJECTIONS OF DICHLORETHYLSULPHIDE

Series of animals, rabbits and dogs, were given varying amounts of dichlorethylsulphide by subcutaneous and intravenous injection. Two samples of very pure dichlorethylsulphide were used, one furnished by Major Moses Gomberg, and the other by the Chemical Warfare Service. For the subcutaneous injections in rabbits, a site on the right side of the back was constantly employed. The hair was clipped or shaved over an area six centimeters in diameter and the liquid dichlorethylsulphide was injected into the subcutaneous fascia above the spinal muscles. In dogs, also, the injection was made beneath the skin of the back. For the intravenous injections in rabbits, the superficial femoral and jugular veins were used. The pure substance was used, instead of oily solutions, because of the great danger of fatty embolism with the latter. In most cases, the animals were allowed to die, but some were killed in order to avoid postmortem change in the tissues. In all cases, autopsies were done, the tissues were fixed in formol, and sections of all organs were stained in hematoxylin and eosin, and other routine stains.

(A) SUBCUTANEOUS INJECTION OF DICHLORETHYLSULPHIDE

The following condensed protocols are selected as representative of the reactions following injection of varying amounts of dichlorethylsulphide. Rectal temperatures, daily weights and character of feces are given, and these, taken together, serve to indicate the severity of the reaction.

RABBIT 55.—Subcutaneous injection of .015 c.c. of dichlorethylsulphide. Very slight general reaction, with apparently complete recovery, except for the local lesion, twenty-six days after injection.

DATE	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Dec. 16	102.3	1870	.015 c.c. dichlorethylsulphide subcutaneously.
" 17	102.5	1750	No diarrhea.
" 18	102.7	1740	" "
" 19	102.6	1870	" "
" 20	103.1	1880	" "
" 21	102.6	1930	" "
" 22	102.6	1950	Slight diarrhea.
" 23	103.2	2010	No diarrhea.
" 24	103.5	1970	" "
" 25	102.6	2010	" "
" 26	102.6	2060	" "
" 27	103.0	2100	" "
" 28	103.3	2200	" "
" 29	104.1	2090	" "
" 30	103.4	2200	" "
" 31	103.1	2130	" "
Jan. 1	102.8	2120	" "
" 2	103.3	2070	" "
" 3	103.0	2140	" "
" 4	102.6	2150	" "
" 5	103.3	2130	" "
" 6	102.8	2090	" "
" 7	103.0	2090	" "
" 8	103.4	2090	" "
" 9	103.5	2150	" "
" 10	102.2	2300	" "
" 11	102.8	2190	No diarrhea. Lesion is now nearly healed. There is a hairless area about 1 cm. in diameter, which is covered with a shiny smooth cicatrix except for a small area in its central portion.

RABBIT 48.—Subcutaneous injection of .03 c.c. of dichlorethylsulphide. Slight general reaction. Living, thirty-seven days after injection, with apparent complete recovery, except for the local lesion.

DATE	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Dec. 5	101.6	2100	.03 c.c. dichlorethylsulphide subcutaneously. No signs of local irritation.
" 6	102.6	2020	No diarrhea. Animal very thirsty.
" 7	102.0	2050	" "
" 8	103.0	2060	" "
" 9	101.0	1990	" "
" 10	101.8	1940	Slight diarrhea.
" 11	103.6	1950	No evidence of diarrhea.
" 12	102.4	1990	Perianal hair somewhat soiled.
" 13	103.6	1900	No diarrhea.
" 14	104.4	1870	" "

DATE	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES (Cont'd from p. 274.)
Dec. 15	103.9	2000	No diarrhea.
" 16	103.2	2030	" "
" 17	102.7	1930	" "
" 18	102.6	1830	" "
" 19	101.6	1810	" "
" 20	102.6	2040	" "
" 21	103.6	2000	" "
" 22	102.2	2080	" "
" 23	102.1	2110	" "
" 24	102.7	2090	" "
" 25	103.3	2000	" "
" 26	101.6	2060	" "
" 27	102.0	2070	" "
" 28	102.3	2150	" "
" 29	103.5	2110	" "
" 30	103.7	2140	" "
" 31	103.6	2170	" "
Jan. 1	103.1	2020	" "
" 2	102.9	2030	" "
" 3	102.8	2250	" "
" 4	103.5	2170	" "
" 5	103.2	2060	" "
" 6	103.4	2020	" "
" 7	103.2	1990	" "
" 8	102.1	2020	" "
" 9	102.6	2060	" "
" 10	102.8	2240	" "
" 11	102.6	2100	No diarrhea. The local lesion is not yet completely healed. There is an indurated area about 1 by 1.5 cm. over which there is an incomplete regeneration of epithelium. This area is firmly adherent to the underlying tissue.

RABBIT 47.—Subcutaneous injection of .03 c.c. of dichlorethylsulphide. Moderately severe reaction. Death on the twelfth day.

	TIME	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Dec. 5		102.5	1520	.03 c.c. dichlorethylsulphide subcutaneously. No evidence of local reaction.
" 6		102.8	1430	No diarrhea.
" 7		102.1	1490	No diarrhea. Edematous area at site of injection measures 2 by 6 cm.
" 8		101.8	1460	No diarrhea.
" 9,	9:30 A.M.	97.6	1380	" "
" 9,	10:30 P.M.	97.0		Hair soiled about anus and soft fecal material on thermometer.
" 10,	9:30 A.M.	98.6	1250	Diarrhea.
" 10,	5:00 P.M.	96.0		"
" 11,	9:00 A.M.	99.0	1120	"
" 11,	5:00 P.M.	96.7		"
" 12,	9:30 A.M.	99.8	1155	"
" 12,	4:30 P.M.	100.2		Hair soiled, but feces formed.
" 13		101.6	1100	No diarrhea.
" 14		101.5	1060	" "
" 15		100.8	1060	" "
" 16		101.7	1070	" "
" 17		97.2	995	Appears much sicker. Perianal hair soiled, but no diarrhea noted.
" 17,	1:00 P.M.			Died.

AUTOPSY

Autopsy at 1:45 P.M. Body warm. No rigor. *Pleural cavities* and *pleuræ* negative. *Heart* contracted. The right auricle still pulsates when stimulated. The *lungs* show a moderate congestion with hypostatic areas posteriorly in the lower lobes. The *liver* is congested, otherwise negative. The *gall bladder* is not distended. The spleen shows a moderate congestion, likewise the *kidneys*, in which there are also some edema and slight cloudy swelling. The *stomach* is nearly empty and the mucosa shows no changes. The upper small *intestines* are slightly edematous. Formed stools are found in the *colon*. No evidence of diarrhea. At the root of the mesentery there is a lobulated mass of edematous hyperplastic lymph nodes.

Microscopic Findings.—*Lungs*. Slight congestion. No edema. *Heart*. Negative. *Spleen*. Congestion. In the sinuses are great numbers of pigmented hemophages, the pigment varying in color from brown to almost black. Hemosiderosis. *Kidneys*. Moderate congestion. Very slight cloudy swelling. Practically negative. *Adrenals*. Negative. *Stomach*. Negative. *Small Intestine*. Congestion and edema of mucous membrane with necrosis of the superficial epithelium of the tops of the folds and villi. Glands of Lieberkühn show excessive mucus formation and individual glands show necrosis. Minute erosions occur along the mucosa. The *liver* shows marked passive congestion, a nutmeg liver with acute central necrosis in many lobules. The bile ducts show an unusual mucous degeneration of the epithelium with edema of the surrounding connective tissue. There is a complete necrosis of the epithelium of the *gall bladder* and of its basement membrane. The neighboring liver tissue also shows a zone of necrosis as from the diffusion of some necrosing substance from the gall bladder. At the *site of injection* there is a large area of necrosis extending through the striped muscle into the fascia. About this, there is a zone of fibroblastic proliferation and leucocyte infiltration. The striped muscle in the neighborhood shows a marked Zenker's necrosis.

Rabbit 50.—Subcutaneous injection of .06 c.c. of dichlorethylsulphide. Moderately severe reaction. Apparent recovery, except for local lesion. Animal killed on the 32nd day after injection.

	TIME	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Dec. 6		101.7°	2020	.06 c.c. dichlorethylsulphide subcutaneously.
" 7		101.8	2000	No diarrhea. Very thirsty.
" 8		101.6	2130	No diarrhea.
" 9		100.0	2060	" "
" 10,	9:30 A.M.	100.9	1990	" "
" 10,	5:00 P.M.	98.6		Perianal hair somewhat soiled.
" 11,	9:00 A.M.	100.0	1920	Diarrhea.
" 11,	5:00 P.M.	98.6		Marked foul diarrhea.
" 12,	9:30 A.M.	99.6	1840	Diarrhea.
" 12,	4:30 P.M.	101.7		Perianal hair still soiled.
" 13		102.6	1790	" " " "
" 14		102.6	1840	Stool slightly soft.
" 15		102.4	1820	" " "
" 16		102.7	1840	Perianal region still somewhat soiled.
" 17		101.8	1710	No diarrhea.
" 18		102.0	1650	" "
" 19		102.3	1640	" "
" 20		102.2	1740	No diarrhea. Quite weak.
" 21		103.0	1710	" "
" 22		101.8	1660	No diarrhea. Weak and appears very sick.
" 23		102.9	1680	No diarrhea. Appears stronger.
" 24		103.0	1650	" "
" 25		103.2	1680	" "
" 26		102.6	1740	" "
" 27		104.0	1780	" "
" 28		102.7	1800	" "

	TIME	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES (Cont'd from p. 276)
Dec.	29	102.9	1810	No diarrhea.
"	30	103.9	1910	" "
"	31	103.6	1950	" "
Jan.	1	103.6	1900	" "
"	2	103.4	1870	" "
"	3	102.9	1910	" "
"	4	103.2	2030	" "
"	5	102.9	1940	" "
"	6	102.7	1930	" "
"	7	102.9	1970	No diarrhea. The local lesion now measures 15 by 30 mm. It is dry, nonpurulent and shows slowly progressing healing.
"	7, 2:30 P.M.			Animal killed. Autopsy at once.

AUTOPSY

Pleuræ, pleural cavities, heart and *lungs* are negative. The *stomach* is distended with food; its mucosa appears negative. The *gall bladder* is small; the bile, pale. *Liver.* Congestion. *Spleen.* Congestion. *Kidneys.* Slight cloudy swelling and congestion. The upper small *intestines* contain a small quantity of thin fluid material. There are no formed stools in the colon, but no evidence of diarrhea. The intestinal mucosa shows no lesions to the naked eye.

MICROSCOPIC FINDINGS.—*Heart.* Negative. *Lungs.* Congestion without edema. Small patches of bronchopneumonia. *Spleen.* Marked congestion with a fairly large number of pigmented phagocytes. *Kidneys* and *adrenals.* Negative. *Stomach.* Negative. Mucosa well preserved. *Liver.* Congestion. Slight cloudy swelling. Bile ducts negative. *Gall bladder.* Epithelium well preserved. No necrosis. *Intestine.* Marked catarrhal enteritis. Epithelium well preserved. No desquamation. Lumen nearly empty. *Pancreas.* Congestion. *Mesenteric lymph nodes.* Extreme edema.

RABBIT 63.—Subcutaneous injection of .06 c.c. of dichlorethylsulphide. Severe reaction. Animal killed on the fifteenth day.

DATE	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Dec. 23	105.0°	2810	.06 c.c. dichlorethylsulphide in deep subcutaneous and intramuscular injection.
" 24	103.6	2770	No diarrhea.
" 25	103.0	2580	" "
" 26	102.0	2610	Slight diarrhea.
" 27	102.1	2580	Diarrhea.
" 28	99.7	2500	"
" 29	98.5	2450	Marked diarrhea.
" 30	100.9	2260	" "
" 31	101.6	2120	" "
Jan. 1	101.8	2130	Diarrhea.
" 2	103.0	2050	Stools formed but moist. Marked edema of right half of abdominal wall.
" 3	102.9	2060	No diarrhea.
" 4	103.4	2100	" "
" 5	103.1	1950	" "
" 6	102.0	1920	" "
" 7	100.5	1840	" "
"	7, 1:30 P.M.		Killed. Autopsy at once.

AUTOPSY

Pleural cavities, pleuræ, heart and *lungs* negative, except for numerous firm, slightly caseous areas at root of right lung, probably an old tuberculosis. *Peritoneal cavity* contains about 50 c.c. of clear fluid. *Liver.* Congestion. *Gall bladder.* Moderately distended with thin bile. *Stomach.* Moderately filled. No visible lesions of the mucosa. *Intestines.* Peristalsis very active. Thin mucoid fluid in upper small intestine. In the cecal pouch there is much thick gruel-like fecal material with denser oval masses adherent to the mucosa. Formed stools in colon. *Kidneys.* Congestion and slight cloudy swelling. *Adrenals.* Congestion. *Mesenteric nodes.* Somewhat hyperplastic.

Microscopic Findings.—*Heart.* Negative. *Lungs.* Pulmonary abscesses. Congestion. *Spleen.* Marked congestion. No pigmented phagocytes. *Kidneys.* Congestion, otherwise negative. *Adrenals.* Excess of fat. Marked lipoidosis of fascicular and reticular zones. *Stomach.* Negative. *Intestines.* Epithelium well preserved for the greater part. No mucoid degeneration except in one portion, where the mucous glands are distended and filled with hyaline cast-like masses. Many of the glands are shallow mucous cysts. *Liver.* Cells small, simple atrophy. *Gall bladder.* Epithelium perfectly preserved. No necrosis. Papillæ less marked than normal. Submucosa edematous. *Site of injection.* Large area of necrotic muscle. Deposit of lime salts. Bacterial infection.

Rabbit 65.—Subcutaneous injection of .12 c.c. of dichlorethylsulphide. Very severe reaction. Death on the fifth day.

TIME	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Dec. 23	104.3°	2750	.12 c.c. dichlorethylsulphide subcutaneously.
" 24	104.9	2580	No diarrhea.
" 25	102.0	2470	Beginning diarrhea.
" 26	102.8	2410	Diarrhea.
" 27	100.8	2310	Slight diarrhea.
" 28	97.2	2200	Very severe diarrhea. Died during the night of Dec. 28 to 29.

AUTOPSY

Body cold. Marked rigor. Entire posterior portion of body is soaked with fluid feces. At the site of injection there is a small brownish area. On incising this area, the subcutaneous fascia is found to be a bright sulphur yellow in color. There is very little local edema. *Pleural cavities* and *pleuræ* are negative. The *heart* shows a slight dilatation. There is a moderate congestion of the *lungs* most marked posteriorly. The *peritoneum* is negative and there is no fluid in the abdominal cavity. The *liver* is firm, deeply fissured, and shows a marked congestion. The *gall bladder* is nearly empty, collapsed, its wall wrinkled. It contains but a few drops of a thin yellowish mucoid fluid. The *stomach* is moderately distended. The stomach mucosa appears negative. The *spleen* and *kidneys* show congestion; otherwise they are negative. *Adrenals.* Negative. The *intestines* contain only fluid fecal material. No lesions of the intestinal tract can be seen. All *splanchnic* veins show a marked congestion.

Microscopic Findings.—*Heart.* Negative. Large white clot in right ventricle. *Lungs.* Intense congestion and edema. Patches of atelectasis. One of the pulmonary arteries contains a large laminated thrombus or embolus, rich in leucocytes. *Spleen.* Intense congestion. In the sinuses there are great numbers of phagocytes containing hemosiderin. *Kidneys.* Congestion, otherwise negative. *Adrenals.* In one adrenal there is an area of fibrosis. *Liver.* Intense congestion. Cloudy swelling. Cirrhosis. Coccidiosis. *Gall bladder* is completely necrotic. Necrotic diffusion zone in surrounding liver tissue. The larger bile ducts show hyaline swelling of their columnar epithelium. Excessive mucus formation. *Stomach.* Postmortem change, otherwise negative, except at the pyloric end, where there is a marked mucoid degeneration. *Intestine.* Extreme catarrh. All glands show extreme mucous degeneration. Desquamation of the epithelium. *Skin lesion.* Large area of necrosis. Hemorrhage. Edema. No reaction.

Rabbit 64.—Subcutaneous injection of .12 c.c. of dichlorethylsulphide. Se-

vere reaction. Death on sixth day. The close parallelism between this case and the preceding is noteworthy.

DATE	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Dec. 23	103.7	2500	.12 c.c. dichlorethylsulphide subcutaneously.
" 24	103.5	2260	No diarrhea. Some edema of abdominal wall on the right side.
" 25	103.1	2210	No diarrhea. Edema continues.
" 26	103.4	2110	" " " "
" 27	103.4	2040	Moderate diarrhea.
" 28	103.2	1920	Slight diarrhea.
" 29	97.6	1830	Marked diarrhea.
			Died during the night of Dec. 29. to 30.

AUTOPSY

Body cold. No rigor. Edema of abdominal wall has diminished. There is a small red-brown eschar at the site of injection. *Heart.* Moderate dilatation. Fibrin and leucocyte clot in right auricle. *Lungs* are somewhat mottled, particularly in upper lobes, probably an early lobular pneumonia. Congestion. *Peritoneum.* Moist shining. *Liver.* Congested. *Gall bladder.* Well filled. Bile, thin and greenish yellow in color. Small *intestines* and greater part of colon distended with very abundant yellowish brown fluid fecal material. Formed stools in descending colon. *Kidneys.* Moderate congestion. *Splanchnic vessels* all show marked congestion.

MICROSCOPIC FINDINGS.—*Heart.* Negative. Large white clot with very few leucocytes. *Lungs.* Purulent bronchopneumonia. Marked congestion and edema. There is a large thrombus of a pulmonary vessel, the wall of which shows necrosis. Around the vessel there is a zone of necrosis which shades off to partial necrosis, as though due to the diffusion of a necrosing substance from the vessel. There are enormous numbers of staphylococci throughout the lung. *Kidneys.* Congestion. Numerous casts in one. *Gall bladder.* Wall completely necrosed, with area of diffusion necrosis in surrounding liver tissue. *Liver.* Congestion. Cloudy swelling. Small areas of lime salt deposit in necrotic liver cells. Some of the larger bile ducts show a polynuclear infiltration around the columnar epithelium. The epithelium itself shows a slight cloudy swelling. *Adrenals.* Increased lipoid content in cortex. Congestion of medulla. *Stomach.* Negative. *Intestines.* Marked desquamative catarrh. Necrosis of upper portion of mucosa. Extreme mucoid degeneration of the glands. *Site of injection.* Enormous area of necrosis extending clear through the skin and subcutaneous tissues. Hemorrhage. Thrombosis. Areas of polynuclear infiltration. Secondary infection.

RABBIT 67.—Subcutaneous injection of .18 c.c. of dichlorethylsulphide. Very severe reaction. Severe diarrhea within 24 hours and death during the third day.

TIME	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Dec. 27, 3:30 P.M.	102.2°	1660	.18 c.c. dichlorethylsulphide subcutaneously.
" 28, 11:00 A.M.	98.2	1570	Marked diarrhea.
			Died during the night of Dec. 28 to 29.

AUTOPSY

Body cold. Rigor mortis present. Head retracted. Fur about the anus is wet with liquid feces. The abdominal wall shows a marked edema which extends up the right flank. At the site of injection the subcutaneous tissues show but very little edema and no surface lesion is visible. Upon incising this area the fascia is found to be yellow in color. *Pleural cavities* and *pleuræ* are negative. *Heart.* Moderate dilatation. Blood

coagulated. *Lungs.* Marked congestion. *Peritoneum.* Moist shining. No free fluid in peritoneal cavity. *Liver.* Congestion. *Gall bladder.* Moderately filled with thin bile. The *stomach* is partly distended. Its wall is somewhat edematous and in the mucosa several minute erosions are visible. *Spleen* and *kidneys.* Congestion. *Adrenals.* Negative. The *intestines* are distended with gas and fluid feces. Marked diarrhea. Splanchnic congestion.

Microscopic Findings.—*Heart.* Negative. *Lungs.* Congestion. Some edema. Areas of atelectasis. *Spleen.* Congestion without pigmentation. *Kidneys, adrenals* and *pancreas.* Negative. *Liver.* Congestion. Slight cloudy swelling. The larger bile ducts show desquamation of the epithelium and some of them are completely necrosed. *Gall bladder.* The wall is completely necrosed and there is some necrosis from diffusion into the surrounding liver tissue. *Stomach.* Negative. *Intestines.* Catarrhal enteritis. Marked mucoid degeneration throughout.

Rabbit 66.—Subcutaneous injection of .18 c.c. of dichlorethylsulphide. Severe diarrhea. Marked fall in temperature. Death on the eleventh day.

DATE	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Dec. 27	103.7°	2550	.18 c.c. of dichlorethylsulphide subcutaneously.
" 28	102.0	2350	No diarrhea. Marked edema of abdominal wall.
" 29	101.6	2320	" " " " " " "
" 30	101.0	2260	" " " " " " "
" 31	99.6	2200	" " " " " " "
Jan. 1	99.4	2160	" " " " " " "
" 2	98.0	2160	No diarrhea. Edema somewhat less.
" 3	97.0	2080	Diarrhea.
" 4	97.1	1890	Marked diarrhea.
" 5	95.0	1610	Marked diarrhea. Left eye sealed with exudate. (Terminal secondary infection.)
" 6	94.0—	1540	Marked diarrhea. Both eyes sealed with mucopurulent exudate. Died during the night of Jan. 6 to 7.

AUTOPSY

Body still warm. No rigor. Both eyes sealed with exudate. When lids are separated, a large quantity of mucopurulent exudate escapes. No superficial lesion at site of injection and only a slight subcutaneous induration can be felt. There is a firm mass, about 2.5 cm. in diameter, in the abdominal wall at the site of the marked edema noted while the animal was living. On incising this mass it is found to be somewhat edematous still, and the tissues are stained a bright sulphur yellow color. *Heart.* Right-sided dilatation. *Lungs.* Pale pink in color. Slight congestion. *Liver.* Marked congestion. *Gall bladder.* Distended. Bile highly pigmented. *Stomach.* Nearly empty; its contents bile-stained and very mucoid. In the mucosa there are numerous small erosions, particularly in the fundus, along the greater curvature. These are covered with an abundant mucus and have shreds of brownish red material, probably blood clot, streaking the mucus over them. *Spleen.* Negative. *Kidneys.* Congestion and slight cloudy swelling. The *intestines* contain gas and a small quantity of fluid material. There are no formed stools. *Adrenals.* Congestion.

Microscopic Findings.—*Heart.* Negative. *Lungs.* Moderate congestion. Emphysema. No edema. *Kidneys.* One kidney shows many casts in the medullary tubules. Otherwise negative. *Spleen.* Markedly congested, with a fairly large number of pigmented phagocytes. *Liver.* Congestion and cloudy swelling. *Stomach.* Extreme mucoid degeneration of the epithelium of the outer portion of the mucosa, with desquamation. Marked cloudy swelling of the parietal cells. Small postmortem erosions. *Gall bladder.* Mucosa fairly well preserved. No necrosis of wall or neighboring liver tissue. *Intestines.* Marked mucoid degeneration. Extreme catarrhal enteritis.

Rabbit 69. Subcutaneous injection of .24 c.c. of dichlorethylsulphide. Diarrhea. Death within twelve hours.

TIME	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Dec. 30, 3:45 P.M.	103.9	1660	.24 c.c. of dichlorethylsulphide subcutaneously. No evidence of local irritation. Died during the night of Dec. 30 to 31.

AUTOPSY

Body cold. Rigor present. Soft formed stools matted in hair about anus. No superficial lesion at site of injection, only a slight subcutaneous edema. Upon incising this area, there is a very strong odor of dichlorethylsulphide. *Heart.* Marked dilatation. *Lungs.* Congestion, with small hemorrhages beneath the pleura of the diaphragmatic surfaces of the lower lobes. *Liver.* Congestion. *Stomach.* Moderately distended. No lesions of mucosa visible. *Spleen, kidneys* and *adrenals.* Congestion, otherwise negative. *Intestines.* Distended with gas and fluid fecal material. No formed stools. Marked splanchnic congestion.

Microscopic Findings.—*Heart.* Negative. *Lungs.* Congestion. Edema. Small capillary hemorrhages. *Adrenals.* Negative. *Spleen.* Congestion. No pigmented phagocytes. *Pancreas.* Negative. *Kidneys.* Rather marked cloudy swelling, even to simple necrosis. *Gall bladder.* Complete necrosis of wall, necrosis extending into liver tissue for some distance. Slight cloudy swelling of the liver cells. *Stomach.* Negative. *Intestines.* Congestion, otherwise negative. *Site of injection.* Large area of necrosis. Edema. No reaction.

Rabbit 70.—Subcutaneous injection of .30 c.c. of dichlorethylsulphide. Diarrhea. Death within twelve hours.

TIME	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Dec. 30. 4:15 P.M.	104.0	1810	.30 c.c. of dichlorethylsulphide subcutaneously. No evidence of local irritation. Died during the night of Dec. 30 to 31.

AUTOPSY

Body cold. Rigor present. Much soft fecal material about the anus. Strong odor of dichlorethylsulphide when area of injection is excised. *Heart.* Marked dilatation. *Lungs.* Congestion, otherwise negative. *Liver, spleen, kidneys* and *adrenals.* Congestion. *Gall bladder.* Well filled. *Intestines.* The upper portion of the small intestine is filled with yellowish fluid material. No formed stools in lower colon. Marked splanchnic congestion.

Microscopic Findings.—*Heart.* Hypertrophy and dilatation. *Lungs.* Intense congestion and edema. *Spleen.* Congestion. Very few pigmented phagocytes. *Pancreas.* Negative. *Adrenals.* Congestion. *Kidneys.* Congestion and some cloudy swelling. *Liver.* Congestion and fatty degeneration. *Gall bladder.* Necrosed. Diffusion zone of necrosis in the surrounding liver tissue. *Intestines.* Epithelium well preserved. Early stage of mucous degeneration; practically every cell filled with mucus and the majority of them intact. *Site of injection.* Large eschar involving all tissues.

Rabbit 72.—Subcutaneous injection of .60 c.c. of dichlorethylsulphide. Death on the second day.

	TIME	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Dec. 31,	3:15 P.M.	102.7°	3050	.60 c.c. of dichlorethylsulphide subcutaneously. No evidence of local irritation. Animal eating in five minutes.
	4:00 P.M.			Sits quietly. Respiration rate appears somewhat accelerated.
	6:00 P.M.	102.5		Quiet. No diarrhea.
	7:30 P.M.	102.0		Quiet. Heart regular. Respiration quickened. Seems to be about to roll over on side, but quickly recovers itself.
	8:30 P.M.	101.7		No diarrhea.
	9:00 P.M.	101.8		" "
	9:15 P.M.			No diarrhea. Hopping about and eating.
Jan. 1,	10:00 A.M.	101.1	3010	No diarrhea.
	11:00 A.M.	102.3		Soft pasty feces.
	2:30 P.M.	102.5		Diarrhea.
				Died during the night of Jan. 1 to 2.

AUTOPSY

Body still somewhat warm. Perianal hair soiled. Very strong odor of dichlorethylsulphide at site of injection. *Heart.* Right-sided dilatation. *Lungs.* Congestion. *Liver, spleen, kidneys* and *adrenals.* Congestion. Otherwise negative. *Stomach.* Moderately distended. In the mucosa there are several small erosions with brownish red bases. *Intestines.* Much fluid material. No formed stools in lower colon. Diarrhea. Edema of *thoracic* and *abdominal walls.*

MICROSCOPIC FINDINGS.—*Brain.* Congestion. *Heart.* Negative. *Lungs.* Congestion without edema. *Spleen.* Intense congestion without pigmented phagocytes. *Kidneys.* Congestion. Otherwise negative. *Stomach.* Negative. Some postmortem change. *Small intestine.* Marked postmortem change, with the picture of a mucous catarrh involving the greater part of the tract. *Liver.* Cirrhosis. Coccidiosis. Large bile ducts dilated; their epithelium well preserved. The small bile ducts are unchanged. Slight fatty degeneration. *Gall bladder.* Nearly complete necrosis of wall. Narrow necrotic zone of diffusion into surrounding liver tissue.

RABBIT 74.—Subcutaneous injection of .60 c.c. of dichlorethylsulphide, .15 c.c. being injected in each of four widely separated areas on the back. Rabbit killed when dying, four hours after injection. No apparent acceleration of reaction with increased opportunity for absorption.

	TIME	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Jan. 1,	11:45 A.M.	103.5°	1970	.15 c.c. of dichlorethylsulphide injected in each of four areas. No evidence of local irritation.
	2:15 P.M.			Lying on side. Moves legs and head readily. Heart strong and regular. The increased irritability, shown by reaction to sound and jarring of table, suggests that due to strychnine.
	4:30 P.M.			Respirations few and gasping. Heart beating vigorously. Diarrhea.
	4:45 P.M.			Killed by chloroform. Autopsy at once.

AUTOPSY

Head somewhat retracted. Perianal region covered with soft fecal material. *Heart.* Moderately dilated. *Lungs.* Negative. *Liver.* Congestion. *Gall bladder.* Nearly empty. Negative. The *stomach* is moderately distended. The mucosa of the fundus, particularly

along the greater curvature, shows a large number of small, shallow erosions with dark red-brown bases. *Intestines.* Contain much fluid material. No formed stools in colon.

MICROSCOPIC FINDINGS.—*Liver.* Marked congestion. Slight cloudy swelling. The small bile ducts are apparently normal. *Gall bladder.* Epithelium perfectly preserved. No changes observable. *Stomach.* Well preserved. Portions examined show no changes. *Intestines.* Catarrhal enteritis.

Dog 3.—White bull terrier, weight 8 kilos. Subcutaneous injection of .24 c.c. of dichlorethylsulphide. Severe diarrhea. Death in four days.

Aug. 27.—.24 c.c. of dichlorethylsulphide injected subcutaneously in back.

Aug. 28.—Appears sick. Is much less active and coat is roughened.

Aug. 29.—Appears very sick. No diarrhea.

Aug. 30.—Very severe diarrhea. Stools fluid and brownish black in color, resembling altered blood. The animal remains quiet.

Aug. 31.—12:00 noon. Lying on side. Respiration slow and shallow. Diarrhea persists.

6:00 P. M. Dog died during the afternoon. Autopsy at 7:00 P. M.

AUTOPSY

The body is in complete rigor. The posterior portion is soiled with fluid fecal material. At the site of injection there is an indurated lamellar area, about 10 cm. in diameter, which involves both skin and subcutaneous fascia. *Pleural cavities* and *pleuræ* negative. *Heart.* Marked right-sided dilatation, the left ventricle being in rigor. Small amount of very dark fluid blood in the chambers. *Lungs.* Free throughout. Air-containing. Middle lobe of right lung congested. No pneumonia. No free gas or fluid in *peritoneal cavity. Omentum* free. The subperitoneal vessels over the *intestines* are congested and there are a few minute subperitoneal hemorrhages. The intestines are empty and firmly contracted. The *duodenum* contains a bile-stained fluid and the mucosa is bile stained. Throughout the small intestine the mucosa shows a marked congestion and there are small hemorrhages in the summits of some of the folds. The Peyer's patches are hyperplastic. In the colon the mucosa is much congested and there are a few very minute hemorrhages. The *appendix* is negative. The *stomach* wall is contracted, the rugæ prominent. The mucosa is much congested and there are a few pinpoint hemorrhages. The *kidneys* show slight cloudy swelling. The *adrenals* are well preserved and negative. The *bladder* is contracted; its mucosa, negative.

MICROSCOPIC FINDINGS.—The *heart* shows dilatation and its vessels are congested. *Lungs.* Marked edema. Intense congestion. Small hemorrhages. Several areas of hemorrhagic infarction, with embolic blocking of the vessels. *Spleen.* Congestion. Atrophy. *Kidneys.* Marked congestion. Slight cloudy swelling. *Pancreas.* Marked cloudy swelling. *Liver.* Cloudy swelling. Marked congestion. Marked mucoid degeneration and cloudy swelling of the epithelium of the smaller bile ducts. All of the bile ducts contain a violet-staining, hyaline substance and the epithelium is higher than normal, the cells appearing larger and swollen. The nuclei appear increased in number. The cytoplasm stains violet, but many of the cells are vacuolated. In a few of the larger bile ducts there are small areas of necrosis. The *stomach* mucosa is intact. There is marked congestion and some increase in mucus in the upper portion of the mucosa. The mucosa of the small *intestine* is congested, edematous, and infiltrated with leucocytes. The epithelium of the glands shows syncytial formations of regenerating epithelium. The columnar form of the cells is lost and there is no mucus formation except in the lower small intestine, where there are many mucous cysts, especially in the deeper portions of the mucosa. The fundi of the glands of Lieberkühn are dilated, filled with stringy mucin or a colloid material. The epithelium is cuboidal, or flattened, or syncytial, and stains a deep violet with hematoxylin and eosin. In some of the dilated glands of Lieberkuhn the epithelium is entirely gone and the lumen is filled with a hyaline cast. The epithelium of the upper part of the glands and of the surface is entirely gone. The picture is that of a severe degenerative and desquamative catarrhal enteritis with beginning regeneration. The lymph follicles are hyperplastic and the germ centers show lymphoid exhaustion. *Mesenteric nodes.* Marked congestion. Great numbers of hemophages filled with blood cells. *Adrenals.* Marked congestion of medulla. *Site of injection.* A large eschar with marked edema. In the vessels there are large thrombi. The borders of the lesion show an abundant polynuclear infiltration and large areas of hemorrhagic extravasation.

(B) SUBCUTANEOUS INJECTION OF HYDROCHLORIC ACID

Since it has been assumed by some that the local and general effects of dichlorethylsulphide are due to the action of the hydrochloric acid produced by its hydrolytic cleavage, a series of animals was given varying amounts of hydrochloric acid by subcutaneous injection. The following protocol is selected as illustrative of this group.

RABBIT 76.—Subcutaneous injection of .60 c.c. of hydrochloric acid. Both local and general reactions entirely unlike those produced by dichlorethylsulphide.

	TIME	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Jan.	3, 9:45 A.M.	103.2°	1600	.60 c.c. of hydrochloric acid subcutaneously. Very marked evidence of local irritation. Marked contraction of superficial and deep muscles. The skin "knots up." In about five minutes, evidences of severe pain cease and the animal is eating.
	4	103.6	1710	No diarrhea. Very extensive lesion at site of injection. There has been complete destruction of the skin and subcutaneous fascia over an area 4 by 5 cm., so that the muscles of the back are fully exposed.
	5	103.4	1600	No diarrhea. The muscle is now exposed over an area 5 by 7 cm. There is a constant oozing of blood from the borders of the deeply excavated lesion.
	6	103.8	1490	No diarrhea. Still some bleeding from wound.
	6, 8:30 P.M.			Killed by chloroform. Autopsy at once.

AUTOPSY

Large excavated lesion, measuring 5 by 7 cm., at the site of injection. The borders are smooth. The base consists of charred, dry fragmented muscle in coarse bundles and masses. There is no purulent exudate. The whole lesion is nearly black in color, as though charred, and is very foul smelling, with the odor of dry gangrene. *Heart.* Still beating. Negative. *Lungs.* Bright pink in color. Moderate congestion. *Liver.* Congested. Extensive coccidiosis. *Spleen.* Negative. *Stomach.* Contains a small amount of food and water, and much swallowed mucus. There are no visible lesions of the mucosa. The *intestines* are nearly empty except the cecum which is moderately filled. The scant amount of fecal matter in the small intestine is very thin, mucoid, and bile stained. In the lower colon the fecal material is soft and but slightly formed. There is, however, no evidence of diarrhea about the anus.

MICROSCOPIC FINDINGS.—*Heart.* Negative. *Lungs.* Congestion. No edema and no hemorrhages. *Liver.* Coccidiosis. No diffusion necrosis into liver tissue around the gall bladder. *Gall bladder.* Epithelium well preserved. No necrosis. No desquamation. Many mucin threads in lumen. *Stomach, intestines, kidneys* and *adrenals.* All negative. *Tissue from site of injection.* Very extensive eschar formation.

(C) SUBCUTANEOUS INJECTION OF DIHYDROXYETHYLSULPHIDE

A series of animals was given varying doses of dihydroxyethylsulphide (hydrolyzed mustard gas) by subcutaneous injection, in order to ascertain whether the severe general effects could be due to the absorption of this substance from the site of injection. The following condensed protocols are selected from this series.

RABBIT 80.—Subcutaneous injection of .30 c.c. of dihydroxyethylsulphide. No local lesion, no diarrhea and no loss of weight.

DATE	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Jan. 8	104.6°	2250	.30 c.c. of dihydroxyethylsulphide subcutaneously. No evidence of local irritation, and animal eats at once when released.
" 9	102.8	2210	No diarrhea. No local lesion.
" 10	102.6	2270	" " " " "
" 11	102.8	2240	" " " " "
" 12	101.9	2250	" " " " "
" 13	102.6	2300	" " " " "
" 14	102.0	2300	" " " " "
" 15	101.6	2280	" " " " "
" 17	104.0	2170	" " " " "
" 18	103.6	2180	" " " " "

RABBIT 81.—Subcutaneous injection of .60 c.c. of dihydroxyethylsulphide. No local lesion. No diarrhea.

	TIME	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Jan. 8,	9:25 P.M.	104.6°	2110	.60 c.c. of dihydroxyethylsulphide subcutaneously. No evidence of local irritation, and animal eats at once when released.
" 9,	8:30 A.M.	103.2	2100	No diarrhea. Very slight edema at site of injection.
	2:30 P.M.			No diarrhea.
	2:45 P.M.			Killed with chloroform. Autopsy at once.

AUTOPSY

There is a slight congestion of all organs. *Stomach* is well filled, its mucosa grossly negative. *Intestines.* Apparently negative. Formed feces in lower colon. No evidence of diarrhea. The *bladder* contains a very turbid yellowish white urine. No other changes.

MICROSCOPIC FINDINGS.—*Lung.* Slight congestion. No edema. *Kidneys.* Negative. Slight congestion. *Adrenals.* Negative. *Spleen.* Negative. *Liver.* Marked fatty change. *Gall bladder.* Epithelium perfectly preserved. No changes. *Small Intestine.* Slight, but well defined catarrh. Congestion of mucosa. Excessive mucus formation. *Stomach.* Negative.

(D) INTRAVENOUS INJECTION OF DICHLORETHYLSULPHIDE

The following condensed protocols are selected from the various series of intravenous injections. In every case in which dichlorethylsulphide was given, it was injected without dilution. Although bland oils will serve as suitable diluents so far as mutual solubility is concerned, the certainty of producing some degree of fatty embolism, with resulting confusion in the pathologic picture, renders this method inadvisable. In addition, the much greater solubility of dichlorethylsulphide in the oil than in the body fluids may be expected to retard its action and delay the production of its characteristic symptomatology.

RABBIT 53.—Intravenous injection of .06 c.c. of dichlorethylsulphide. General convulsions. Marked reduction of temperature. Prostration. Death in less than three hours.

	TIME	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Dec. 9.	2:50 P.M.	101.5	1570	.06 c.c. of dichlorethylsulphide given intravenously in superficial femoral vein. Light chloroform anesthesia. Animal made quick recovery from anesthesia, soon moving about.
	3:50 P.M.	94.0		Animal very much weaker. Respiration very rapid. Easily startled by sudden movements or unexpected noises. Slight convulsive movements. No general convulsion.
	3:54 P.M.			First general convulsion, consisting of irregular rapid movements. There is some opisthotonos but the head is drawn chiefly to one side.
	4:15 P.M.			Lies on side. Occasional convulsions.
	4:45 P.M.			Continues to lie on side. Can not turn over. Jerking movements of forepaws, head and neck. Salivation and lacrimation. Pupils dilated. Respiration slow and irregular.
	5:30 P.M.			Death. Much stringy saliva during last fifteen minutes.
	8:00 P.M.			Autopsy.

AUTOPSY

Body nearly cold. Rigor mortis marked. Abdomen moderately distended. No diarrhea. *Pleural cavities* and *pleuræ* negative. *Heart.* Moderately dilated, particularly on the right side. Dark fluid blood, clotting tardily. *Lungs.* Air-containing throughout. Congestion moderate, except posteriorly. *Spleen.* Negative. *Kidneys.* Slight congestion. *Adrenals.* Negative. *Liver.* Marked congestion. Lobules large. Central zones dark red, outer two-thirds of lobule, grayish red. *Gall bladder.* Well filled with a pale mucoid bile. *Stomach.* Distended with food. Mucosa shows scattered areas of postmortem change along greater curvature. Upper small *intestine* contains a thin yellowish mucoid fluid. Lower small intestine is well filled and there are formed stools in the lower colon.

Microscopic Findings.—*Central Nervous System.* Congestion. *Heart.* Negative. *Lungs.* Congestion. Atelectasis. No edema. No hemorrhage. *Spleen.* Marked congestion but no pigment. *Adrenals* and *pancreas.* Acute congestion. *Stomach.* Slight cloudy swelling of parietal cells. Congestion. *Intestines.* In portion examined the mucosa is well preserved. Congestion of villi. No necrosis. *Liver.* Moderate congestion. Slight fatty degeneration.

Rabbit 51.—Accidental intravenous injection of dichlorethylsulphide in the course of a deep subcutaneous injection. Total injection .12 c.c., of which probably less than .06 c.c. entered a small subcutaneous vein. Convulsions. Diarrhea. Death in four hours.

AUTOPSY

Body still warm but rigor mortis is present. Soft fecal material from anus. Posterior portion of body is much soiled with feces. *Pleural cavities* and *pleuræ.* Negative. *Heart.* Right-sided dilatation. Blood, fluid, clotting slowly. *Lungs.* Free. Slight congestion. Air-containing throughout. *Spleen.* Negative. *Kidneys.* Moderate congestion. *Adrenals.* Negative. *Liver.* Moderate congestion. *Stomach.* Distended with food. The first portion of the small *intestine* contains a very abundant slightly yellow fluid, which is somewhat mucoid. In the descending colon and rectum there are no formed stools.

Microscopic Findings.—*Heart.* Negative. *Lungs.* Moderate congestion. No edema. Small patches of atelectasis. Bronchioles dilated. No hemorrhages. *Spleen.* Moderate congestion without many pigmented cells, although there are a few. *Kidneys.* Congestion. *Intestine.* Mucosa well preserved. *Stomach.* Negative. *Liver.* Congestion. Slight cloudy swelling.

(E) INTRAVENOUS INJECTION OF HYDROCHLORIC ACID

RABBIT 89.—Intravenous injection of .06 c.c. of hydrochloric acid. Animal living on fourth day. No diarrhea. No evidence of general reaction.

	TIME	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Jan. 16,	11:45 A.M.	103.0°	1520	.06 c.c. of strong hydrochloric acid (diluted to 1.20 c.c. with distilled water) in jugular vein.
	1:00 P.M.			Apparently well.
Jan. 17		102.4	1710	No diarrhea.
" 18		103.4	1680	" "
" 20		104.6	1600	No diarrhea. Perfectly well.
" 20				Killed. Autopsy at once.

AUTOPSY

Gross findings all negative, except thrombosis of jugular at site of injection.
MICROSCOPIC FINDINGS.—All negative, except for thrombophlebitis at site of injection.

(F) INTRAVENOUS INJECTION OF DIHYDROXYETHYLSULPHIDE

RABBIT 87.—Intravenous injection of .30 c.c. of dihydroxyethylsulphide. Animal living on the fifth day. No diarrhea. No marked loss of weight.

	TIME	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Jan. 15,	4:00 P.M.	101.6°	2410	.30 c.c. dihydroxyethylsulphide into jugular vein. Light chloroform anesthesia.
	7:00 P.M.			Animal eating. Apparently well.
Jan. 16		103.9	2350	No diarrhea.
" 17		102.6	2320	" "
" 18		102.4	2320	" "
" 20		102.3	2350	No diarrhea. Perfectly well.
" 20				Killed. Autopsy at once.

AUTOPSY.—All gross findings negative.
MICROSCOPIC FINDINGS.—Negative, except for marked fatty liver.

SUMMARY OF EXPERIMENTAL WORK

Subcutaneous Injections.—When pure dichlorethylsulphide is injected subcutaneously in doses of from .015 up to .60 c.c., the injections are apparently painless and the animals exhibit no signs of discomfort. Even with the largest doses the animals resume feeding as soon as released and give no evidence of local irritation. At varying periods of time, from one hour to several days, depending in part upon the size of dose, and in part upon the rate of absorption, toxic symptoms appear, usually in the form of salivation, diarrhea and marked depression of temperature. At first the respirations are quickened; later they become slow. From the largest doses the animal may die within two hours, without diarrhea, but with a short period of nervous excitement followed by coma and gradual failure of respiration. Doses of from .015 to .06 c.c. are

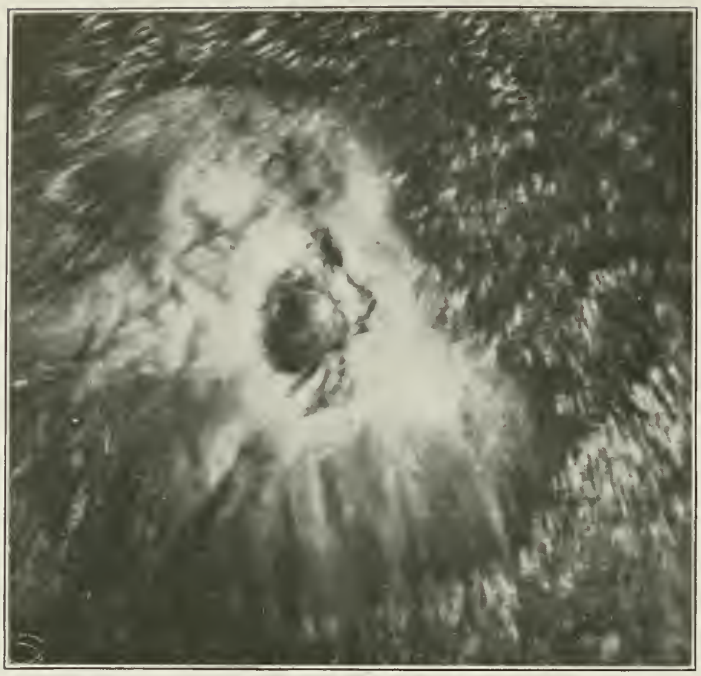

Fig. 1.—Rabbit 58. Eschar resulting from subcutaneous injection of .03 c.c. of dichlorethylsulphide, eighteen days after injection.

Fig. 2.—Rabbit 62. Eschar resulting from subcutaneous injection of .06 c.c. of dichlorethylsulphide, eleven days after injection.

not necessarily fatal to rabbits, although a certain proportion of the animals receiving such doses do die. Death from these doses usually takes place from the fourth to the tenth day. Diarrheal symptoms may appear as early as the second day, but in the great majority of cases diarrhea does not appear until the fourth to seventh day. Coincident with the diarrhea there is a marked fall of temperature, which may be as much as seven to eight degrees below normal. If the animal survives the diarrheal period, the temperature may come back nearly to, or quite to, normal, to fall again just before death, if the animal dies. During the diarrheal stage the animal rapidly loses weight and this loss of weight continues after the cessation of diarrhea, so that when the animal dies, it may

Fig. 3.—Rabbit 76. Sloughing lesion produced by subcutaneous injection of .60 c.c. of hydrochloric acid, twenty-four hours after injection.

have lost as much as one-third of its body weight. The diarrheal stools are fluid, mucoid, brown to black, sometimes tarry, and very foul smelling. Accompanying the diarrhea, there is a marked anorexia and great thirst; the animal is quiet, depressed; and both circulation and respiration are slowed. In the animals that recover, the diarrhea may last for several days, accompanied by a marked lowering of temperature and a general depression. As the stools become normal the temperature rises and the general condition improves until the animal is again apparently perfectly normal.

At the site of the subcutaneous injection there developed a local edema which is usually much less than the edema produced by cutaneous applications. In

a certain number of cases, there is a marked edema of the belly wall, although the injections were routinely made on the back of the animal, apparently due to the hypostasis of body fluid containing mustard gas, from the seat of the injection. The edematous area at the seat of injection gradually changes into an indurated eschar (see Figs. 1 and 2) which undergoes a slow demarcation from the neighboring living tissue. In some animals injected subcutaneously with the dichlorethylsulphide furnished by the Chemical Warfare Service and living two days or longer, a sulphur-yellow coloration of the tissue at site of injection was noted. Such a coloration was not noticed in any animal injected with the Gomberg preparation.

The gross pathology shown by animals killed or dying at varying periods

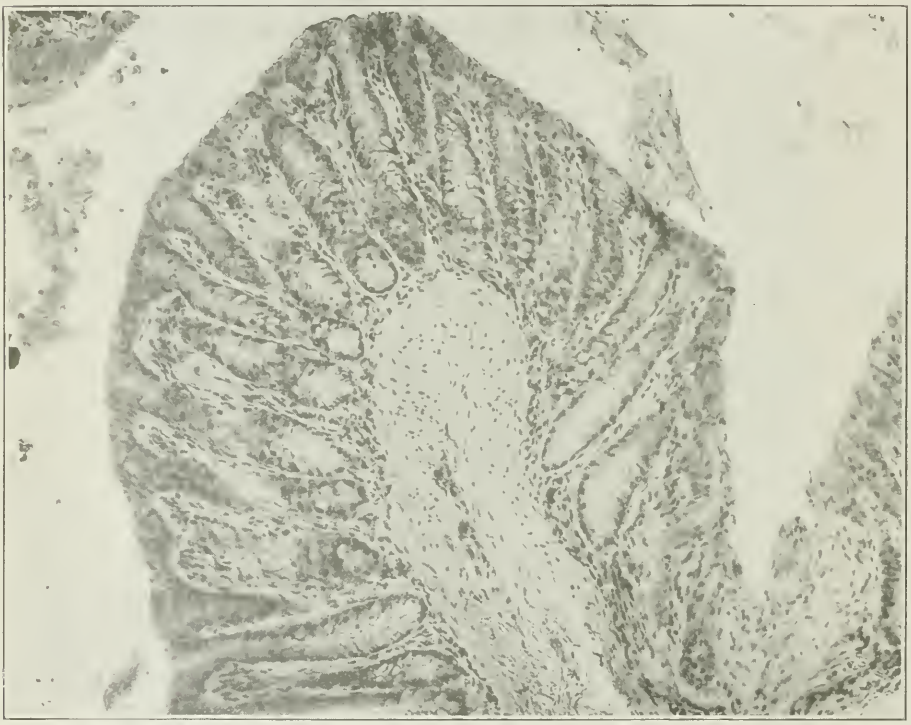

Fig. 4.—Rabbit 59. Received subcutaneous injection of .045 c.c. of dichlorethylsulphide. Died on third day during mild diarrhea. General mucoid degeneration.

after subcutaneous injections consists of a general passive congestion of all organs with occasional minute hemorrhages, emboli, and infarctions. The most specific changes are those found in the gastrointestinal tract in the form of an intense splanchnic congestion and a more or less severe catarrhal enteritis. In practically every instance it was noted that the contents of the gall bladder consisted of a thin, pale, yellowish, mucoid bile.

The microscopic findings confirm the gross appearances. No specific changes are found in any organs except the intestines, spleen, and possibly the bile ducts. These specific changes consist in a mucoid degeneration, necrosis, and desquamation of the epithelium of the intestinal mucosa, marked congestion

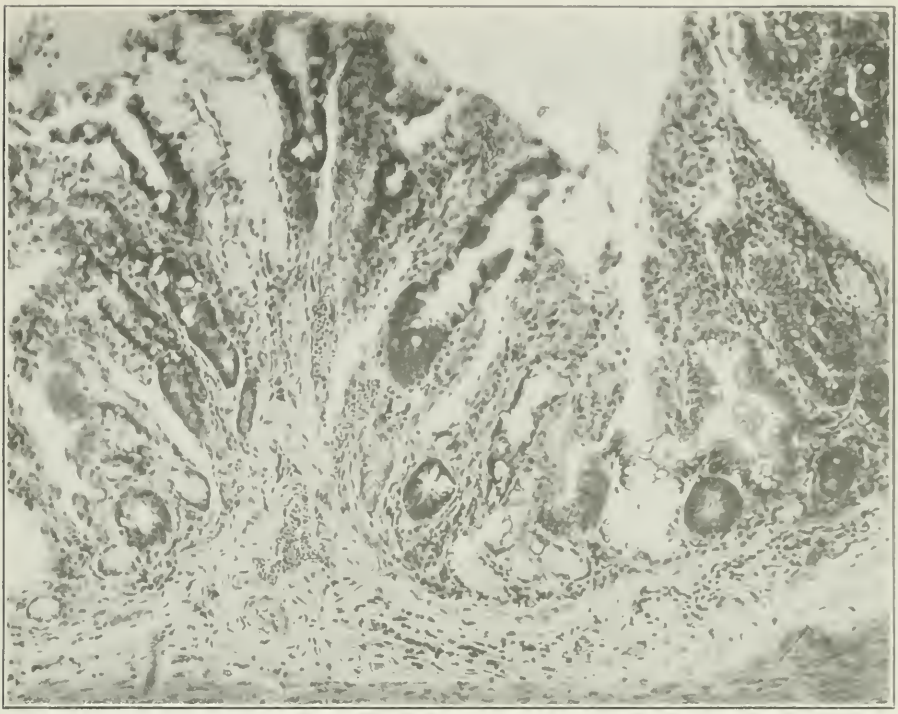

Fig. 5.—Rabbit 66. Received subcutaneous injection of .18 c.c. of dichlorethylsulphide. Began to have diarrhea seven days after injection and died four days later. Section of upper portion of small intestine showing acute catarrhal enteritis.

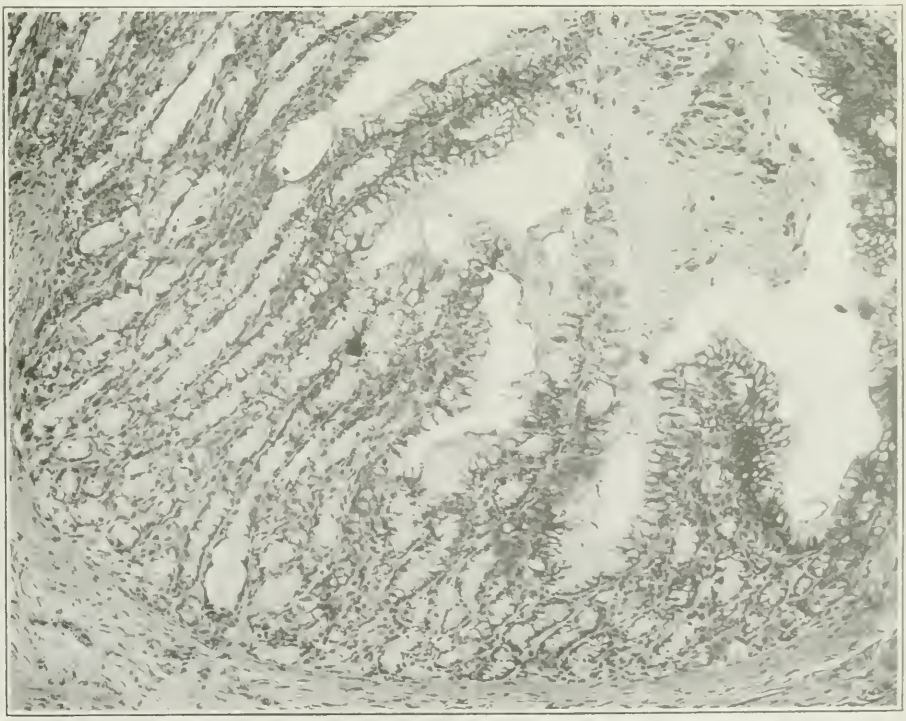

Fig. 6.—Same rabbit as preceding. Extreme mucoid degeneration. Catarrhal enteritis. Mucous diarrhea.

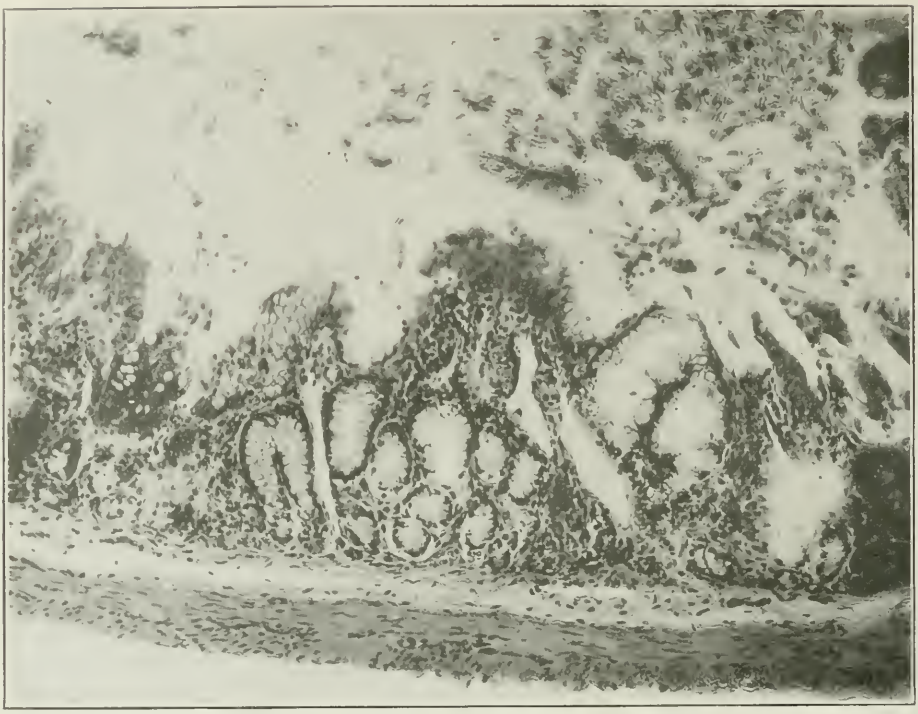

Fig. 7.—Section of cecal wall from same rabbit as preceding. Marked catarrhal inflammation. Mucous diarrhea.

Fig. 8.—Rabbit 65. Received subcutaneous injection of .12 c.c. of dichlorethylsulphide. Diarrhea began on the second day, the animal dying three days later. Extreme mucoid degeneration of the entire intestinal epithelium. Mucous diarrhea.

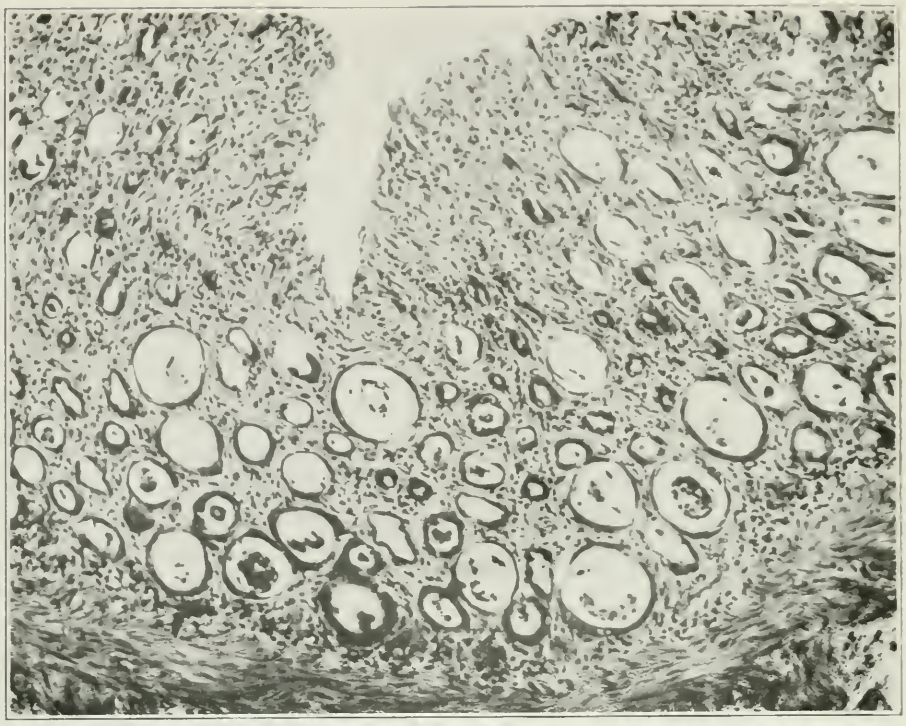

Fig. 9.—Dog 3. Received subcutaneous injection of .24 c.c. of dichlorethylsulphide. Died in four days with a very severe diarrhea. Extreme catarrhal desquamative enteritis. Mucoid degeneration and necrosis of the glandular epithelium.

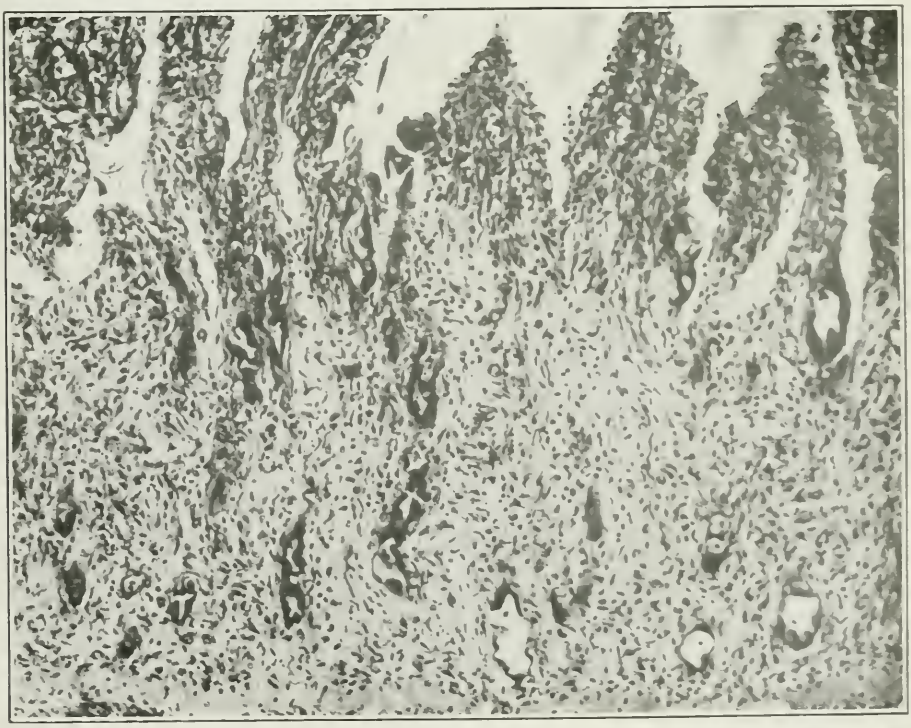

Fig. 10.—Same dog as preceding. Middle portion of small intestine showing desquamation of the superficial epithelium and necrosis of the epithelium of the glands of Lieberkühn. Severe enteritis.

Fig. 11.—Rabbit 63. Received subcutaneous injection of .06 c.c. of dichlorethylsulphide. Severe diarrhea from fourth to ninth day. Killed fifteen days after injection. Mucosa of intestine intensely congested and edematous. Marked mucoid degeneration with cystic glands. Regeneration of superficial epithelium.

Fig. 12.—Rabbit 50. Received subcutaneous injection of .06 c.c. of dichlorethylsulphide. Very severe diarrhea on fifth to seventh day afterwards. Apparent recovery. Killed on the thirty-second day after injection. Mucosa shows excessive mucus formation.

of the whole splanchnic area, with edema, and occasional petechial hemorrhages and minute erosions of the mucosa. Degenerative changes have also been noted in the epithelium of the bile ducts, and the postmortem changes in the mucosa of the gall bladder and larger bile ducts appear to be greatly hastened, and more severe than normal, as though from the presence of some necrosing substance in the bile. (See Figs. 4 to 13.) A very striking feature of the pathology of many cases of subcutaneous injections of dichlorethylsulphide is the presence in the blood spaces and sinusoids of the spleen of great numbers of large pigmented phagocytes and hemophages containing altered red blood cells, indicating a greatly increased hemolysis. (See Fig. 13.)

The microscopic appearances of the tissues at the site of injection are those

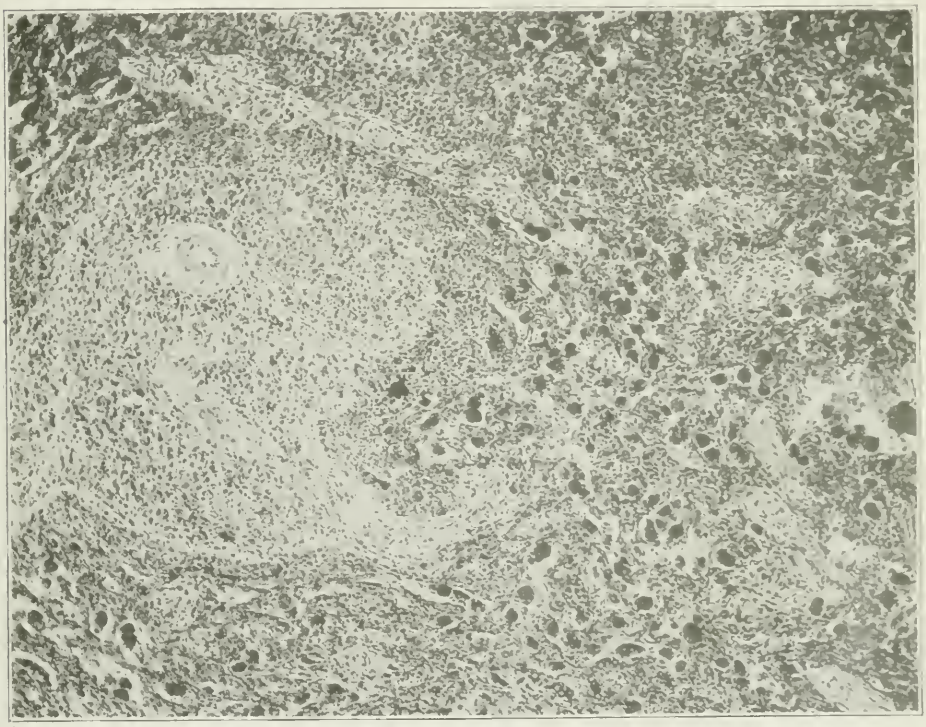

Fig. 13.—Rabbit 47. Received subcutaneous injection of .03 c.c. of dichlorethylsulphide. Very severe diarrhea on fourth to eighth day. Died on twelfth day after injection. Intestines showed severe catarrhal enteritis. Section of spleen showing the great number of pigmented phagocytes in the blood sinuses.

of an extensive eschar extending entirely through the skin and fascia, and deep into the muscles with extensive extravasations and infiltrations of leucocytes. The appearances of secondary infection are frequently added to those of the primary lesion. In several instances deposits of lime salts were noted in the necrotic area.

Intravenous Injections.—When dichlorethylsulphide is injected directly into the external jugular or superficial femoral veins in doses varying from .0075 to .18 c.c., the animal shows no signs of pain and returns to eating, but within a short time begins to show symptoms of hyperexcitability in the form of very

rapid respiration and slight convulsive movements. Within an hour there may be general convulsions and opisthotonos with head turned to one side. The animal quickly becomes very weak, tends to lie upon its side with rapid jerking movements of the legs, as though running. The animal can not turn over. Soft feces are frequently involuntarily discharged. The animal acts as though nauseated and there are slight salivation and lacrimation. The pupils are dilated. The temperature rapidly falls six to eight degrees before death. The convulsions cease, the pupils contract, salivation increases, the animal passes into coma, and there is a gradual failure of circulation and respiration, although the respiration ceases some time before the heart stops beating. Death usually takes place in one to four hours, depending upon the size of the dose. Following the intravenous injection of larger doses, the first convulsive movements may appear in ten minutes and be followed rapidly by wild clonic convulsions, very much resembling those of rabies.

The gross pathologic changes following intravenous injections of dichlorethylsulphide are dilatation of the heart, particularly on the right side, and marked congestion of the lungs with numerous petechial hemorrhages. All other organs show congestion with numerous minute hemorrhages. Mucosa of gastrointestinal tract is covered with thick mucus, is congested, and may show minute hemorrhages. The contents of the gall bladder may be a thin and pale bile. No specific changes were found in the brain and cord and no thrombus in the vein at the site of injection.

Microscopic examination confirms the gross appearances, in that it shows extreme congestion, stasis and hemorrhages in the lungs; congestion of the gastrointestinal tract, with an increased formation of mucus scattered irregularly throughout, not comparable, however, to the changes found in animals injected subcutaneously; and marked general congestion.

EPICRISIS

The introduction of dichlorethylsulphide into the blood stream causes death within a few hours with characteristic symptoms. When injected subcutaneously, with resulting slower absorption into the circulation, death occurs later, from twelve hours to several days, likewise with a characteristic symptomatology. The symptoms may be classed roughly as (1) nervous and (2) intestinal. In the case of large doses, with death occurring within an hour, the nervous symptoms may alone be exhibited, while in the animals living for some time the nervous symptoms are slight and those of the intestinal group predominate. In the correlation of the pathologic findings with the symptomatology, no change has been found in the central nervous system offering an adequate explanation for a death dependent entirely upon a lesion of the central nervous system. In the delayed cases (subcutaneous) the intestinal tract offers a pathologic picture commensurate with the symptoms. In addition to the specific pathology just mentioned, incidental pathologic findings in the form of thrombi, emboli, embolic infarctions and hemorrhages may at times be interpreted as explaining some of the observed clinical phenomena.

Of all the pathologic lesions produced by mustard gas, apparently the most specific and most interesting are the intestinal changes following intravenous and subcutaneous injections. The intense catarrhal enteritis observed after such injections suggests the excretion of dichlorethylsulphide or some product of its decomposition through the intestinal mucosa. No changes have ever been observed in the kidneys, indicating the excretion of any toxic product through the renal epithelium. In the case of the liver there have been observed, at times, degenerative changes in the biliary epithelium, suggesting the presence of some injurious substance in the bile. Further, the probability of this hypothesis seems the greater in view of certain changes, found in a certain proportion of cases, in the gall bladder, in the form of an apparently earlier postmortem necrosis of the gall bladder wall, and a diffusion of the bile into the neighboring liver tissue. It has been a notable observation that, in many cases, when autopsy was performed immediately upon death of the animal, such early postmortem change was found in the gall bladder; while in animals that had not received dichlorethylsulphide injections, such an immediate postmortem change was not observed.

A large number of experiments were made in the effort to demonstrate the presence of mustard gas or its products in the intestinal wall and contents, and in the liver and bile. In the tissues at the site of the injection, the odor of mustard gas will persist for several days and cutaneous applications of the ether extract of these tissues will produce a well-marked mustard burn, even when the ether extract is much diluted. Further, in one case in which death occurred within one hour after jugular injection, with numerous small embolic hemorrhages in the lungs, the odor of mustard gas was clearly evident on section of the lung, and an ether extract of the lung gave a slight positive test. With this single exception we have been unable to obtain any odor of mustard gas or any positive skin reaction from extracts of any organ. Ether and aqueous extracts of the liver and bile, the intestinal tract and its contents, the blood, heart and lungs, and of the urine, even when concentrated, have yielded no odor of mustard gas and have given no positive skin test.

It has been generally assumed that the injurious action of mustard gas follows its hydrolysis in the living cells and tissues. The products resulting from the hydrolysis of dichlorethylsulphide are hydrochloric acid and dihydroxyethylsulphide.

From Major Moses Gomberg of the Chemistry Department of the University of Michigan a quantity of pure dihydroxyethylsulphide was obtained. Varying series of experiments made with this substance showed it to be apparently inert, both as applied locally, by ingestion, and by subcutaneous and intravenous injections, in quantities up to many times the lethal doses for dichlorethylsulphide. No diarrhea, no fall in temperature, and no other symptoms were produced, and no pathologic lesions were found in such animals with the exception of marked fatty changes in the liver cells.

A similar set of experiments with hydrochloric acid injections was also carried out. The subcutaneous injection of hydrochloric acid, even in a dose

of .12 c.c. produces intense local irritation and pain, in striking contrast to the anesthetic action of dichlorethylsulphide. The course of the local lesion is entirely unlike that produced by mustard gas. The liquefaction of the eschar is very rapid and there quickly results a deep excavated lesion, the bottom and sides of which appear charred. (See Fig. 3.) No diarrhea is produced; the temperature remains normal or rises; no systemic symptoms are produced, and the animal will recover unless secondary infection sets in.

The intravenous injection of .06 c.c. of hydrochloric acid (diluted to prevent local injury during injection) produces no symptoms comparable to those resulting from the intravenous injection of dichlorethylsulphide.

The manner of causation of the intestinal lesions remains the special problem of the pathology of dichlorethylsulphide poisoning. Neither hydrochloric acid nor dihydroxyethylsulphide, when introduced into the circulation, will cause similar changes. Therefore these lesions can not be the result of the action of hydrochloric acid produced at the site of the lesion and circulating in the blood. The next most plausible explanation of the cause of the intestinal lesions is that mustard gas itself or some other unknown decomposition product circulates in the blood and is excreted through the mucosa of the intestine, or possibly, also, through the bile.

It has been stated that the most delicate chemical test for mustard gas is a color reaction with a solution of platinic chloride and sodium iodide. The liquid to be tested is applied to absorbent paper moistened with this solution. In the presence of dichlorethylsulphide the pink color is changed to a faint purple, which becomes blue or deep blue, depending upon the concentration of the mustard gas solution. When this test was applied to ether and aqueous extracts of the liver, bile and intestine from animals injected subcutaneously and intravenously with dichlorethylsulphide, we obtained a definite blue color more marked in the case of the aqueous extracts. This reaction we at first believed to be a positive test for mustard gas in these extracts. Continuing our control experiments, we found that the dihydroxyethylsulphide gives the same reaction with the platinic chloride-sodium iodide as dichlorethylsulphide. The test is, therefore, not a specific one for pure dichlorethylsulphide. We then took the aqueous extracts of liver, bile, intestine and urine, which might be expected to have the dihydroxyethylsulphide in them, if it were present at all, since it is soluble in water, and heated them with concentrated hydrochloric acid with the expectation of reconverting the hydrolyzed product into mustard gas. The products thus obtained, however, gave no odor of mustard gas, and their ether extracts neither gave a skin reaction nor a positive color test. On the other hand, these aqueous extracts of body fluids and organs did give bluish green color tests with the test solution that might be interpreted as faint positive reactions for mustard gas. Unfortunately, however, the aqueous extracts of these same organs and fluids from animals untreated with mustard gas produce an identical color reaction. We have, therefore, been unable to demonstrate the presence of mustard gas or its hydrolyzed products in the liver, bile, intestines, feces, blood or urine.

CONCLUSIONS

1. Dichlorethylsulphide when injected internally in doses of approximately .06 c.c. per kilo for the rabbit, and .03 c.c. per kilo for the dog, causes a fatal intoxication, characterized, when death occurs quickly, by symptoms referable to the central nervous system; but when death takes place more slowly, by intense diarrhea, anorexia and reduction of temperature.

2. The only specific pathology of such fatal poisonings is a marked degeneration of the epithelium of the gastrointestinal tract in the form of a severe catarrhal enteritis, and the occasional occurrence of similar changes in the epithelium of the bile ducts and gall bladder.

3. These changes suggest the excretion of mustard gas or some poisonous product resulting from its decomposition into the gastrointestinal tract. No positive proof, however, of this mode of excretion could be obtained. The hydrolysis of mustard gas circulating in the blood may take place in the intestinal mucosa, thereby producing the degenerative changes seen in these cells. On the other hand, the intestinal conditions may not be due to the direct action of any substance upon the epithelium of the mucosa, but may be secondary to the splanchnic congestion and the hyperexcitability of the nervous centers.

4. It seems probable that the characteristic symptoms and death following subcutaneous and intravenous injections of dichlorethylsulphide are due to the direct action of this substance circulating in the blood, upon the central nervous system, either with or without hydrolysis in the nervous tissue affected. The specific character and constancy of the symptomatology offer sufficient argument against any assumption that the process is embolic in character.

IV. SUSCEPTIBILITY

In Meyer's first laboratory experiments with dichlorethylsulphide he noticed an apparent difference in individual susceptibility, in that he, himself, was not affected by exposure to it, while a laboratory worker engaged in making it developed conjunctivitis and a severe skin eruption. Meyer's conclusion that individual susceptibility must vary greatly seems hardly warranted by this observation. Undoubtedly Meyer was working with a very impure compound, the concentration of which must have varied from time to time, and the laboratory worker must have been much more exposed to its fumes than Meyer, himself. Further, the dissemination of mustard gas is such an insidious matter of physical conditions and pure chance, that in a group of workers exposed to apparently identical conditions the greatest diversity of effects may be produced, leading to an incorrect supposition of especial resistance or susceptibility in the individual members of the same group. The question of the existence of individual susceptibility can, therefore, be settled, only by the application of experimental methods in which the conditions of exposure are identical.

This has been done by *Marshall, Lynch, Smith*, and *Williams* (Medical Division, Chemical Warfare Service Reports, Nos. 288, 290, 302, 303, 320). These workers found that the results of uniform skin tests showed that there does exist a decided individual difference in the skin reaction to mustard gas

independent of changes in sensitivity due to sweating, etc. About 20-40 per cent of the white men tested showed a certain degree of resistance; while 78 per cent of negroes tested showed a similar resistance. About 2 per cent of the white individuals showed a hypersensitivity; no hypersensitive cases were found among negroes. There exists, then, a much greater degree of cutaneous sensitivity to mustard gas among white people than in the colored race. Groups of individuals treated at different times do not show any great change in sensitivity from time to time. In Report 316, *Marshall, Miller, Reed* and *Beaver* state that in the gassing chamber very little difference in susceptibility has been noted in the dog, monkey, goat, rabbit, guinea pig, and mouse. So far as the conjunctiva and respiratory mucous membrane is concerned there appears to be little or no variation in individual sensitivity. In Report 328, *Marshall* and *Williams* in a study of sensitivity in different animals in their reaction to the skin test found the horse most sensitive and monkeys most resistant, the dog most closely approaching man in percentage of reaction. Individual differences in sensitivity were also noted in animals. An acquired hypersensitivity to mustard gas vapor as the result of previous or repeated burns is claimed by many workers, and accepted by some observers. That such a localized susceptibility may be shown in scars, healing burns, injured conjunctiva and mucous membranes, is very probable, but there is no evidence to the effect that exposures to mustard gas increase the individual's susceptibility on the part of the whole organism.

The individual human sensitivity is in part a racial one, and, therefore, intrinsic and constitutional. *Marshall* (Chemical Warfare Service Reports) would explain it as due to differences in the skin, cutaneous lipoids, etc. Among the individuals of the same race showing differences in cutaneous sensitivity to mustard gas he noted no other constitutional differences or peculiarities. In the cases seen by us there were five individuals who seemed to be cutaneously hypersensitive, as shown by their receiving frequent and severe burns from vapor exposures not affecting other workers so severely, although apparently similarly exposed. The two fatal cases belonged to this group. It is noteworthy that all five of these cases presented constitutional stigmata or clinical symptoms of a definite pathologic constitution, the *thymicolymphatic*.

Autopsy on one case showed a persistent thymus and characteristic lymphoid hyperplasia with exhaustion of the germ centers. The fact that individuals possessing this constitution are especially susceptible to skin conditions, such as eczema, to food idiosyncrasies, to asthma and pollen intoxications, to death from anesthesia, slight surgical operations, slight thermal burns, etc., and to death from acute infections, makes it very probable that a large number of the hypersensitive to mustard gas may possess this constitution. As its chief features can be easily recognized by a good clinician, and as many of its features can be brought out by the clinical history, all workers in mustard gas should be subjected to an examination for the existence of this constitution, and those possessing it should be rejected.

The chief objective features of the constitution are a short, full neck, rounded thighs and hips, evidences of rachitis, pasty or pale complexion, ten-

dency to mouth breathing, adenoids and enlarged tonsils, palpable lymph nodes. Occasionally these features are combined with the tuberculous habitus, long narrow flat thorax, floating ribs, long belly, low scrotum, etc.

In the clinical history the following points should be noted: tendency to croup, laryngeal stridor, asthma, hay fever, unusual tendency to bronchitis, severe reaction to acute infectious diseases, food and drug idiosyncrasies (lobster, crab, egg, honey, strawberries, raspberries, milk, cocoa, tea, morphine, chloroform, quinine, etc.),severe serum reactions, severe anaphylactic phenomena, tendency to eczematous conditions of the skin, goiter, tendency to faint on slight cause, sensitiveness to shock. At autopsy enlarged thymus and hyperplastic lymph nodes are found.

The determination of this constitution is not difficult; and an investigation should be made as to its frequency in those individuals hypersensitive to mustard gas.

FINAL SUMMARY OF DICHLORETHYLSULPHIDE INVESTIGATION

This paper, the sixth in number, closes the series of investigations on dichlorethylsulphide carried out during the last year in the Pathological Laboratory of the University of Michigan. Begun as an independent war research problem, the laboratory later, through Dr. Warthin, became associated with the Medical Advisory Board of the Chemical Warfare Service, and abstracts and preliminary reports of these investigations are included in the Reports of that service. All of the articles have been published in full in this Journal (*Pathology of the Skin Lesions*, May, 1918; *Pathology of the Ocular Lesions*, October, 1918; *The Treatment of Dichlorethylsulphide Injuries*, ibid.; *The Clinical Pathology of Dichlorethylsulphide Poisoning*, November, 1918; *Lesions of the Respiratory and Gastrointestinal Tracts*, this number). In this, the final article, it seems advisable to assemble the main points of knowledge gained by the investigation in the form of the summary given below. The research, which has been carried out in a most intensive manner, involving an immense amount of labor, has been made possible only through the enthusiastic cooperation of the entire laboratory staff, and to these, especially to Dr. Harriet Taylor, we wish to give appreciative thanks. To Major Moses Gomberg, Professor of Chemistry in the University of Michigan, we owe, first of all, our opportunity to take up this research, inasmuch as he, in the beginning, furnished us with a quantity of the purest mustard gas we have been able to obtain from any source. With the dichlorethylsulphide made by him, an absolutely colorless liquid possessing but a faint odor, we have been able to standardize our entire series of investigations; at the same time we have compared its results with those of other samples less pure, obtained from the Chemical Warfare Service and elsewhere. To Dr. Gomberg we owe thanks also for a quantity of pure dihydroxyethylsulphide. To the Regents of the University of Michigan we are also indebted for a special grant of funds for necessary expenditures for animals and additional technical assistants. Finally, to Miss Frances Dunbar, we wish to give our thanks for her care and skill in printing our photomicrographic plates.

SUMMARY

1. *Dichlorethylsulphide ("Mustard Gas")*, in liquid or in vapor form, even in very low concentrations, is an escharotic poison for the animal tissues (skin, conjunctivæ, cornea, mucous membranes of respiratory and gastrointestinal tracts) with which it comes in direct contact. The degree of the injury is proportionate to the concentration of the gas, the time of exposure, individual susceptibility, and local physical conditions, such as moisture, sweating, warmth, pressure and friction. The escharotic action is, for the greater part, painless, the anesthetic effect being especially notable upon the skin; while upon the mucous membranes its action may be more irritant, probably chiefly reflex in character. The cutaneous surfaces most susceptible are those with thinner, more delicate skin, well supplied with sweat glands and hair follicles, where sweat may collect, and which are exposed to friction or pressure, such as the axillæ, flexor surfaces, genitals, inner surface of arms and corresponding surface of trunk, inner surfaces of thighs, between the fingers, etc. There is a penetration of the gas into the sweat and sebaceous glands. The injuries are particularly striking in their insidious, slowly progressive development, becoming first apparent only some hours after the exposure. Upon human skin the lesion appears as a hyperemia, followed by vesication, eschar formation, sloughing, and slow healing, with more or less pigmentation. Depilation may occur; in severe cases the eschar may extend entirely through the corium into the subcutaneous tissues. Secondary infection and gangrene of the eschars occurs invariably in cases not properly treated. Milder lesions may show only the earlier stages of hyperemia, vesication or pigmentation. In general the injuries may be classed as burns of first, second, or third degree. Following extensive hyperemias in human skin a most marked pigmentation, exceeding in degree the most marked forms of solar tan may be quickly developed and fade slowly. This pigmentation may be diffuse or spotted. In human skin vesication is pronounced; in animals the cutaneous lesions are characterized by the development of marked subcutaneous edema in the injured area. The fluid of the vesicle or of the edema is nonirritating when applied to uninjured areas. In the case of human skin frequently exposed to very dilute concentrations (only perceptible by odor), an eczematous itching condition between the fingers, on the genitals, etc., may develop; rubbing or scratching of the itching part may lead to the quick development of a blister or superficial eschar. Such interdigital lesions in laboratory workers may resemble clinically those produced by the itch mite. Cutaneous areas injured by mustard gas are rendered more susceptible to trauma or other forms of injury, including new exposures to mustard gas. This local susceptibility is, however, a general one, and not a specific lowered resistance to the action of dichlorethylsulphide. Subcutaneous injections of pure dichlorethylsulphide produce painless eschars, followed by dry sloughing, with edema less marked than in the case of external cutaneous application; a hypostatic edema may develop on the animal's belly when injected in the back. In the tissues at the site of the injection and in the hypostatic edema mustard gas may be present for some days after the injection. The resolution of mild

skin injuries is often attended by troublesome itching. Healing of the deep cutaneous eschars is very slow; large scars may be produced resembling those resulting from deep thermal burns. The hairs may be lost; but when regenerated they may be white in color.

Upon the cornea mustard gas exerts an especially injurious action, particularly at the vertex. Within ten to fifteen minutes after exposure to dilute concentrations, degeneration or necrosis of the corneal surface may be demonstrated by the application of a 2 per cent alkaline aqueous solution of fluorescein, the injured cells retaining a greenish fluorescent coloration. In more severe injuries the cornea may be killed throughout its entire thickness at the vertex. The mildest cases show a slight cloudiness; the severe cases present a characteristic porcelain appearance of bluish white opalescent cloudiness, often with a more opaque band or line running horizontally across the cornea just below its transverse diameter. The injury to the conjunctiva is shown by the development of a more or less severe catarrhal, seropurulent or purulent conjunctivitis with marked edema of the subconjunctival tissues leading often to "ruffling" of the lids, entropion, ectropion, or a combination of these. Even the lighter cases tend to run a chronic course with disturbances and reduction of vision. In the severe cases cicatrization and vascularization of the cornea take place slowly with resulting impairment or loss of vision. The injured eye is more susceptible to infection; and in infected cases suppurative panophthalmitis may develop with complete destruction of the eyeball. Recovered cases of mild mustard gas conjunctivitis often show an increased sensitivity to the action of light, dust, and other irritants, including mustard gas fumes.

Upon the mucosa of the respiratory tract mustard gas vapor produces a local injury to the epithelium as shown by the development of a catarrhal, desquamative, membranous, diphtheritic or purulent inflammation (rhinitis, stomatitis, pharyngitis, laryngitis, tracheitis and bronchitis), these lesions being most severe in the nose, back of tongue, palate, pharynx and larynx, decreasing in intensity downwards. Coryza, salivation, dryness of mouth and throat, aphonia and persistent cough are the chief symptoms, with physical signs of laryngeal, tracheal and bronchial involvement, and atelectasis and edema of the lungs. As a result of secondary infection a purulent bronchopneumonia may develop.

Through the swallowing of air, saliva or secretions from the upper respiratory tract containing mustard gas, or from the ingestion of contaminated food local corrosive action upon the alimentary mucosa may be produced, varying from a catarrhal inflammation to large areas of eschar formation with resulting gastric ulcer, perforation, etc. The symptomatology of the mildest lesions is covered up by that resulting from the more severe burns elsewhere; the more severe ones will produce marked symptoms referable to the stomach and intestines.

II. There exists a racial and an individual susceptibility to the action of dichlorethylsulphide, particularly in the case of the skin, and probably also in the respiratory tract. The individual susceptibility, in some cases at least, is

associated with the constitutional stigmata and symptomatology of the thymicolymphatic constitution. Acquired susceptibility is not specific.

There is no evidence of any systemic poisoning by the absorption of dichlorethylsulphide from the skin, eyes or mucous membranes of the respiratory or gastrointestinal tracts. There is no metastatic action of the gas from the site of local external application.

In all severe cases of mustard gas burns of skin, eyes, or mucous membranes there is usually the clinical picture of severe shock, in the form of intense pallor, depression of pulse and temperature, general collapse, nausea and vomiting. The mildest cases show no systemic reaction.

No changes are observable in the blood or urine of mild cases. In cases with large infected burns of skin or respiratory tract, the blood presents a mild secondary anemia with leucocytosis; the blood urea is increased; the urine is diminished, concentrated, and contains casts and albumin. Under forced fluids the urinary symptoms improve, and the blood urea diminishes. In severe infected cases the general picture may be that of a severe toxemia.

When injected intravenously or subcutaneously dichlorethylsulphide is an active poison, causing death in one to four hours intravenously and two hours to three weeks after subcutaneous injections (for rabbits intravenous injections of .0075 c.c. per kilo may be lethal within four hours), according to size of dose, individual animal, etc. When death takes place quickly, the symptoms are chiefly those of an action upon the central nervous system, such as hyperexcitability, rapid respirations, general convulsions, opisthotonos, gradual failure of respiration and circulation, coma and death. When the animal lives longer after small intravenous injections, or after subcutaneous injection, there develops a characteristic symptomatology of salivation, marked diarrhea, and fall of temperature, with marked anorexia, emaciation and depression. With subcutaneous injections of .015 to .06 c.c., death usually takes place from the fourth to the tenth day.

III. The specific microscopic pathology of the local lesions of dichlorethylsulphide poisoning consists in degeneration and necrosis of the cells with which it comes in contact. The earliest microscopic change is pyknosis of the nucleus and cell body, followed by hydropic degeneration, liquefaction or coagulation necrosis. In the skin, hyperemia, with regeneration of the damaged cells, vesicle formation, desquamation of the dead epidermis or eschar formation mark varying stages of severity of the lesion. The degenerative changes extend deepest in the hair follicles and sweat glands. In severe burns the necrosis may extend entirely through the corium. In the cornea, pyknosis and simple or coagulation necrosis of the corneal epithelium and interstitial substance, even to the endothelial layer, in extent varying with the degree of exposure, constitute the microscopic features. On the conjunctivæ the epithelium shows pyknosis, hydropic degeneration, liquefaction necrosis, or there may be a deeper necrosis extending into the subconjunctival tissues. The conjunctival surface suffers to a less degree proportionately than the epidermis. On the mucous membranes the epithelium shows pyknosis, hydropic or mucoid degeneration, desquamation, liquefaction or coagulation necrosis. The necrosis

may extend into the submucosa, but the depth of the lesions on the conjunctivæ and the mucous membranes of the respiratory tract is never so great from identical exposures, as it is in the skin. Following the necrosis there is marked hyperemia, and the development of an edema, more marked in the subcutaneous and subconjunctival tissues in animals, but less marked in man. The blood vessels in the necrotic area are killed, the blood cells hemolyzed without thrombus formation or much extravasation, except minute hemorrhages by diapedesis. Following the lesion there is a demarcating inflammation, with slow regeneration, repair or cicatrization. On the mucous membranes there results in the severe cases a localized eschar or ulcer, or a more diffuse diphtheritis. With secondary infection the inflammatory process becomes purulent or suppurative. The influence of secondary trauma and infection is well shown in the early development of deep areas of decubitus in the injured regions of the skin. Multiple furuncles may develop, or large cutaneous areas become gangrenous. In the eye purulent involvement of the anterior chamber, iris and ciliary body may occur, or even a suppurative panophthalmitis. In the respiratory tract secondary infection of the injured mucosa may lead to a purulent bronchopneumonia.

The internal organs in animals with mustard gas lesions of the skin, eyes, respiratory or gastrointestinal tract offer nothing of a specific pathologic nature. There is general congestion, marked splanchnic congestion, acute catarrh of the intestines and, in infected cases, some cloudy swelling of the kidneys.

In fatal cases the cause of death is to be found in shock, secondary infection with toxemia, or local conditions as laryngitis, tracheitis, bronchitis and bronchopneumonia. It is also possible that the entrance into the body of shell fragments carrying liquid dichlorethylsulphide might cause a relatively speedy death through absorption.

At the site of subcutaneous injections there is found a local eschar with demarcating hemorrhage, edema and inflammatory infiltration; in the large veins into which injections have been made, no changes have been found except occasional thrombosis.

The general pathology of the injected cases presents a specific pathologic picture in the intestinal tract in the form of a severe mucoid, desquamative or necrotic enteritis, the intestinal epithelium showing the most marked hydropic or mucoid degeneration, even to liquefaction necrosis. Similar changes may be found in the epithelium of the bile ducts. In the other organs no pathologic changes but congestion have been found, with the rare exception of emboli or thrombi.

IV. The cause of death in intravenous and subcutaneous injections would appear to be the direct action of minute quantities of free dichlorethylsulphide or some poisonous product resulting from its decomposition, upon the cells of the central nervous system. It has been assumed that the pathologic action of dichlorethylsulphide is due to its hydrolysis within the tissue cells. The products of this hydrolysis, hydrochloric acid and dihydroxyethylsulphide, when injected into the blood, do not produce the same effects. Dihydroxyethylsulphide and hydrochloric acid, when injected into the circulation in much

larger doses than would result from the hydrolysis of the fatal doses of mustard gas, are harmless. The effect upon the cells of the central nervous system may, however, depend upon the hydrolysis in these cells of minute quantities of mustard gas in the circulation, or these cells may be injured without such hydrolysis occurring. It is probable that the gastrointestinal catarrh resulting from the injections of dichlorethylsulphide is secondary to the nervous injury, rather than to an excretion of the poison or poisonous products through this tract. No positive tests for dichlorethylsulphide or dihydroxyethylsulphide have been obtained in the bile, intestinal contents, or urine. Incidentally, it has been shown that the platinic chloride-sodium iodide color test for dichlorethylsulphide is not applicable to the body fluids or extracts of various organs and tissues, as similar color changes are produced by some of these.

V. The principles of treatment to be applied to mustard gas injuries are primarily those that will remove any of the gas remaining, prevent infection, and promote healing. Our experience leads us to recommend the use of Dakin's solution in irrigation or full baths for the skin lesions, and a 0.5 per cent solution of dichloramine-T for the eye lesions, and also as a mouth wash. The fluid intake should be forced when the urine is concentrated. Pressure must be removed from all injured areas. Air-excluding and infection-including protections, such as oily dressings, paraffin sprays and coatings, zinc stearate, olive oil, vaseline, etc., should not be used, unless there is an active and persistent germicidal agent present as in the case of sodium stearate impregnated with chloramine–T, or the chlorcosane solution of dichloramine–T.

VI. As to its use in warfare, mustard gas is a disabling rather than a killing agent. Under the actual conditions of the field the great majority of mustard gas casualties are likely to be of a nature tending to incapacitate the injured for service for a number of days or weeks, or even for months. Added to this, the insidious character of this invisible fire, painless and often unrecognized in its action, makes mustard gas a potent factor in undermining the morale of the troops exposed to it.

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EDITORIALS

Influenza and Pneumonia at Camp Grant

CAPTAIN Edwin F. Hirsch and Technician Marion McKinney have made a most thorough study of the influenza epidemic at Camp Grant. They close their report with the following summary:

1. An epidemic of unusual virulence swept with great rapidity through several organizations in Camp Grant between September 21, 1918, and October 18, 1918. During this time 9,037 patients were admitted to the Base Hospital, representing about one-fourth of the strength of the camp, and of these, 26 per cent developed pneumonia. About 11 per cent of the total admissions, or 43 per cent of the total cases of pneumonia died.

2. From the throat cultures of the early admissions pneumococci were recovered with remarkable constancy, influenza bacilli were found exceptionally.

3. Postmortem examinations of those dying during the epidemic demonstrated with great regularity a massive bronchopneumonia.

4. In cultures of the diseased lung, heart's blood, exudates, fluids, and other diseased foci of the body, pneumococci were the predominating organisms.

5. In 50 per cent of the cases of pneumonia, blood cultures demonstrated the presence of pneumococci unmixed with other organisms.

6. Pneumococci in pure culture were recovered from infected sinuses of the head, middle ears, conjuctival and empyema exudates.

7. Experimental inoculation of pneumococci isolated during the epidemic into laboratory animals, demonstrated an exceedingly great virulence for these organisms.

8. Control throat cultures made from German prisoners in the camp, but who escaped the epidemic, showed no pathogenic organisms.

9. The number of German prisoners whose throats were cultured was fifty, and in 50 per cent of these pneumococci were found, but in only three did this organism prove pathogenic to laboratory animals.

10. All strains of pneumococci isolated during the epidemic were tested for their virulence in white mice. Minimal quantities of 24-hour cultures were found highly lethal in susceptible animals. Comparatively small fractions of 24-hour blood agar slant cultures were fatal to rabbits and guinea pigs. The virulence of these strains is considered sufficient to account for the epidemic.

11. One hundred ninety-eight autopsies studied bacteriologically gave the following results:

(a) In the Lungs:	
Pneumococcus pure	89
Pneumococcus and other organisms	55
Hemolytic streptococcus	19
Other organisms	4
Unsatisfactory and not cultured	31
Total	198
(b) In the Heart's Blood:	
Pneumococcus pure	53
Hemolytic streptococcus	23
Pneumococcus and hemolytic streptococcus	1
Other organisms	2
Negative	109
Not taken	10
Total	198

12. The types of pneumonia were distributed as follows:

Type	Number	Per cent
(a) In the Heart's Blood:		
I	5	7.46
II	45	67.16
IV	17	25.37
(b) In the Lungs:		
I	12	6.
II	109	54.2
III	2	1.
IV	78	38.8
(c) In the Spinal Fluid:		
I	3	25.
II	7	58.3
IV	2	16.7

13. The following are the gross pathologic changes found in autopsy:

(a) Extensive bronchopneumonia.
(b) Slight serofibrinous pleuritis.
(c) Acute catarrhal bronchitis and tracheitis.
(d) Acute hyperplasia of the spleen, parabronchial, mesenteric and biliary lymph glands.
(e) Marked cloudy swelling of the myocardium and the parenchymatous organs.
(f) Marked loss of the yellow of the adrenal cortices.
(g) Acute fatty changes of the liver and kidneys.
(h) Multiple petechial hemorrhages of the serous surfaces.
(i) Jaundice.
(j) Acute catarrhal conjunctivitis.
(k) Slight acute serous pericarditis.
(l) Moderate generalized passive hyperemia.

14. In one hundred ninety-eight autopsies, the lobes involved were as follows:

(a) Left lower	149
(b) Right lower	141
(c) Left upper	83
(d) Right upper	119
(e) Right middle	81

—*V. C. V.*

Notes on Influenza

INFLUENCE of Length of Service.—The fatality of the epidemic was greater among those recently brought into the service. This is illustrated by the following abstract taken from a report made by Lieut. Wilson D. Wallis at Camp Lee. This report shows that while those who had been in the service less than one month constituted only 9.19 per cent of the total strength, they furnished 30.11 per cent of the total deaths from influenza and consequent pneumonia. Furthermore, it is shown that while those who had been in the service from one to three months constituted 45.18 per cent of the camp, they furnished 46.24 per cent of deaths. On the other hand, those who had been in the service more than three months constituted 45.63 per cent of the population and furnished only 23.69 per cent of deaths.

Lieut. Wallis says:

"These figures show a much greater percentage of deaths for the first month in camp than the corresponding proportion of the population would warrant; while in the period of three months or more of service, the percentage is less than half of that of the camp population having this length of service. The only approach to a correspondence is in the period from one to three months where the respective percentages differ but little. The increase in length of service is accompanied by a progressive decrease in the percentage of deaths from 30.11 per cent to 27.41 per cent to 18.87 per cent, although only 9.19 per cent of the population in the camp falls within the class of less than one month's service.

"The incidence of mortality is in the first month's service more than three-

fold the percentage of the number of men; and in the period of three months or more of service is scarcely more than half of the percentage of the number of men of the camp in that group."

The fact that the case mortality is higher among those who came from rural homes than among those who came from cities, seems to hold even after three months of service, or more.

The 34th Division which was then in camp at Cody during the preceding Winter and Spring was in Camp Dix, New Jersey, when the epidemic broke out in September, 1918. This Division was composed of fairly well-seasoned men, but the death rate in the Division was 18.70 per cent per thousand as compared with that of 17.21 of men from the 811th Pioneer Infantry composed largely of those fitted only for limited service. It is suggested by the officer making the report that this is due to the fact that such a large proportion of the 34th Division came from rural districts.

The case fatality at Camp Dix among those who came from cities with a population of 10,000 or more, was 10.8; while among those who came from more rural homes the rate was 15.8, although the average service of both groups was the same.

Clinical Features.—The clinical features as described by Majors Synnott and Clark of Camp Dix may be abstracted as follows:

"The usual history was one of gradual onset with prodromes for four or five days prior to admissions,—consisting of headache, malaise, backache, myalgia, fever and chills or chilly sensations, and marked prostration. There was a history of anorexia, and of aggravation of symptoms, after drill or exercise. Occasionally the onset was sudden, sharp and severe. On admission there was cough, often with rusty sputum, a temperature of 103° F., occasionally hyperpyrexia, respirations of 28 to 30, pulse between 80 and 120, a low temperature in a severe case was an unfavorable sign. The blood count showed usually leucopenia. The urine contained albumin and casts. The patients looked very sick, but often did not feel so. Few complained of sore throat or the early sticking pains in chest, aggravated by coughing, so commonly observed in beginning pneumonia.

"The outstanding feature of the disease was the extreme toxemia noted in the serious cases. We could predict almost from the first inspection the outcome of each case. There has been a sharp line of demarcation between the serious and mild cases. Many of the former developed a cyanosis early in the disease and died promptly, after periods varying from a few hours to three days after admission.

"The cyanosis appeared early and was progressive. It was a fairly constant and characteristic symptom in the severe cases. This intense cyanosis was a striking phenomenon. The lips, ears, nose, cheeks, tongue, conjunctivæ, fingers, and sometimes the entire body partook of a dusky, leaden hue. Frequently this cyanosis was apparent before there were any demonstrable physical signs of pneumonia. The cause could not be ascertained, a few spectroscopic readings failing to show absorption bands of methemoglobin. As autopsy revealed marked so-called compensatory emphysema in these cases and as cyanosis is a

common accompaniment of emphysema, possibly this was in some wise accountable for the condition.

"The disparity between temperature and pulse was striking. Patients with temperature between 104 and 106 not infrequently had a pulse below 80. This we regard as a strong point in differential diagnosis between these influenzal pneumonias and those of pure pneumococcic origin.

"The disease was a veritable plague. The extraordinary toxicity, the marked prostration, the extreme cyanosis and the rapidity of development stamp this disease as a distinct clinical entity, heretofore not fully described.

"It is entirely different from our previous pneumonia epidemics. It is fair to state that it is primarily a profound, rapidly progressing septicemia and toxemia, in which pneumonia is an important but somewhat secondary factor."

Influenza and Pneumonia in the Year 1917.—Relying solely upon the sick and wounded cards, there was no relation between influenza and pneumonia in 1917. There are some most competent medical officers who believed that influenza was prevalent in an unrecognized form in the camps in the Fall of 1917, and that a large percentage of the cases of pneumonia occurring at that time were preceded or ushered in by influenza. This belief is apparently founded upon the observations of one or two men, and can be proved or disproved in no way so far as I can see.

Taking the sick and wounded cards for 1917 we can construct the following table:

PNEUMONIA AS A SEQUEL TO RESPIRATORY DISEASES

(All troops in United States in 1917)

PRIMARY DISEASES	NO. OF CASES	NO. OF CASES FOLLOWED BY PNEUMONIA	% OF CASES FOLLOWED BY PNEUMONIA
Measles	47,573	2,075	4.37
Scarlet fever	1,966	54	2.75
German Measles	8,982	39	0.43
Bronchitis	41,233	20	0.049
Influenza	32,248	19	0.059
Meningitis	1,027	13	1.27
Tonsillitis	43,021	7	0.016
T. B. pulmonary	6,799	6	0.088
Laryngitis	4,633	2	0.043
Diphtheria	1,163	1	0.086
Mumps	21,725	0	0.000
Pharyngitis	8,096	0	0.000

In contrast to the above, the following table gives the numerical relation between influenza and pneumonia during the four months of September, October, November, and December, 1918:

Number of cases of influenza	338,343
Number of cases of influenza followed by pneumonia	50,700
Number of deaths from influenza-pneumonia	17,700

INFLUENZA AND PNEUMONIA AS REPORTED IN THE UNITED STATES VITAL STATISTICS FOR EACH YEAR INCLUDING AND SINCE THE YEAR 1900

YEAR	ANNUAL DEATH RATES FROM PNEUMONIA	INFLUENZA	COMBINED DISEASES
1900	158.6	22.8	181.4
1901	133.5	32.2	167.7
1902	124.7	10.1	134.8
1903	122.6	18.5	141.1
1904	136.3	20.2	156.5
1905	115.7	18.8	134.5
1906	110.8	10.3	121.1
1907	120.8	23.3	144.1
1908	98.8	21.3	120.1
1909	96.3	13.0	109.3
1910	147.7	14.4	162.1
1911	133.7	15.7	149.4
1912	132.3	10.3	142.6
1913	132.4	12.2	144.6
1914	127.0	9.1	136.1
1915	132.7	16.0	148.7
1916	137.3	26.4	163.7

Epidemic of Influenza in 1915-16.—During the year 1916, as is seen from the table, the annual death rate from influenza as reported, reached the rate of 26.4 per 100,000. The literature of that time shows that this epidemic originated in the West, first attracted attention in Denver, and gradually spread over the country.

Dr. Dublin of the Metropolitan Life Insurance Company gives the following table in which the deaths from influenza and pneumonia during the months of December, 1914, and January, 1915, are compared with deaths from the same cause during the months of December, 1915, and January, 1916:

NAME OF CITY	DEATHS REPORTED AS DUE TO INFLUENZA		DEATHS REPORTED AS DUE TO PNEUMONIA	
	In 15-16	In 14-15	In 15-16	In 14-15
Baltimore	57	12	219	101
Cincinnati	81	2	105	84
New Orleans	97	44	35	29
New York	494	62	2067	1207
Philadelphia	324	62	564	272
Providence	38	3	31	31
TOTAL	1091	185	3021	1733

Dr. Dublin states that the Industrial Department of the Metropolitan Life Insurance Company covering the entire country and embracing ten millions of people, had deaths in the periods above mentioned as follows:

In December, 1914, and January, 1915 the number of deaths attributed to influenza was	165

While in the corresponding months of 1915-16, the deaths attributed to influenza were	957
The deaths attributed to pneumonia in December, 1914, and January, 1915, were	1468
While the number of deaths attributed to the same cause in December, 1915, and January, 1916, was	2563

Coffey and others have reported an epidemic of influenza at Worcester, Massachusetts, during the first three weeks of January, 1916. During the first three weeks of January, 1915, there were reported in the city of Worcester, twenty-two deaths from respiratory diseases, making a total of 14.9 per cent of the total deaths. In the same period of 1916 there were reported in the city of Worcester, ninety-three deaths from acute respiratory diseases in the same population.

The Relation of Influenza and Antityphoid Vaccination Reactions.—In a general way severe reactions of antityphoid vaccinations resemble in symptomatology, influenza. This led to the suspicion on the part of many medical officers that antityphoid vaccinations in some way increased the susceptibility to influenza. Indeed, some went so far as to say that antityphoid vaccination caused influenza. On account of this suggestion, antityphoid vaccination was discontinued for a time after the appearance of the epidemic of influenza in the Fall of 1918. There were, therefore, entire organizations in which antityphoid vaccination was not practiced. These organizations suffered quite as severely as those which submitted to the vaccination.

The following is an abstract from a report made by the Camp Surgeon at Grant:

"The organizations which suffered most severely were the 5th Limited Service Regiment, the 1st Training Unit and the 13th Training Battalion. These organizations practically were made up of the September increments. Inoculations of new recruits were discontinued. None of the men of the 13th Training Battalion received inoculations and still 3.9 per cent of this command died of pneumonia following this disease. The difference in mortality rate between the 5th Limited Service Regiment, the 1st Training Unit and the 13th Training Battalion, is slight; but the difference between these three organizations and the others is well marked. That the new recruit is more susceptible to this disease and is more apt to succumb than the man who has been trained and accustomed to army life, there is no doubt."

—*V. C. V.*

Pulmonary Tuberculosis and Postural Treatment

IT was pointed out by Webb, Gilbert and Forster that the victim of pulmonary tuberculosis was not infrequently observed resting and sleeping on the side of the least diseased lung. The more actively tuberculous lung would then be

uppermost and so through many long hours be responsible for most of the aeration.

These workers found it of undoubted value to train the consumptive to sleep and rest on the side of the more actively tuberculous organ.

Colonel G. E. Bushnell, M.C., U. S. Army, called the attention of the writer to an observation easily made with the fluoroscope. With a subject lying on one side and the x-ray apparatus properly adjusted the movements of the diaphragm and thorax can be readily studied.

It is noticed that the upper ribs of the recumbent side are pressed together and that there is little motion of this part of the chest wall. Below, however, the diaphragm is noticed to make a far greater sweep on the recumbent than on the upper side.

If the tuberculous lesions are limited to the upper lobe as is usually the case or even should they extend to the apex of the lower lobe, rest of the individual lung by posture would certainly be indicated. In addition the more rapid flow of lymph produced by the greater movement of the diaphragm on the recumbent side would tend to safeguard the lower lobe from tuberculous involvement.

Positive basal lesions, rare except in advanced pulmonary tuberculosis would conceivably be harmed by such postural therapy.

The simple question of the side preferred for rest and sleep has never been properly studied in regard to the pneumonias, bronchiectases and other chest conditions.

The study of the chest movements in different postures by means of the fluoroscope is worth the while and the time of all clinicians who interest themselves in pulmonary conditions.

—G. B. W.

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ORIGINAL ARTICLES

THE DIAGNOSIS OF ACIDOSIS*

A Review and Criticism of the Methods at Present in Use

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THERE has been some confusion in medical literature concerning the exact meaning of the term "acidosis," so that it will be advantageous to preface our discussion of the subject with a brief review of the work upon which the present-day definition is based. The discoveries that large quantities of oxybutyric and oxyacetic acids are excreted in the urine of patients suffering from diabetic coma, and that there is a general similarity between the symptoms of this condition and those which follow the intravenous injection of strong acids (acid intoxication) in laboratory animals, were primarily responsible for the adoption of the term. In seeking earlier signs of acidosis than the actual symptoms of coma, however, examination of the urine for oxybutyric and acetoacetic acids or their oxidation product, acetone, was found to be of uncertain value, since these substances might also appear in decidedly large amounts in the urine of nondiabetic individuals. During starvation, for example, either complete or involving carbohydrate foods alone, acetonuria was frequently met with, which made it clear that the excretion of acetone bodies could not in itself be taken as a reliable indication of impending acidosis.

It was attempted therefore, to develop methods of diagnosis depending, not on the detection of the particular acids, but on the effects which might be produced by the accumulation in the organism of acids in general.

In the first place it was natural to expect that the blood would become

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less alkaline as the result of the acid production, and attempts were therefore made to measure the alkalinity of the blood by titrating with standard acid until the point of neutrality was reached, as judged by the change of tint of some indicator. It was hoped that the values obtained by this method would indicate in the blood of cases threatened with acidosis, the presence of more acids than in normal blood; that is, that a smaller amount of standard acid would require to be added to the former, than to the latter blood, in order to cause the tint of some indicator to change. Although with certain modifications this method is theoretically sound, it was found to have little practical value, partly because it requires large amounts of blood, and partly because the coloring matter has to be removed before the test can be applied. Moreover, it came to be recognized that the amount of added acid, with the indicators ordinarily used, would represent, not only the basic constituents that combine with acids in the quantities in which these could be produced in the organism, even under abnormal conditions, but also those, like proteins and phosphates, that might be called upon to functionate as bases when the limits of acidity compatible with life were greatly overstepped.

It became necessary to seek for some other type of reaction which acids might set up in blood, and the well-known effect which these have in expelling carbon dioxide from its combinations with alkalies was investigated (Walter). It was found by experiments on animals that a marked diminution in the CO_2 content of blood was induced by intravenous injections of acids, and the same was observed to be the case in the blood of patients in diabetic coma (Naunyn).[1] In the light of more modern research, by which, as we shall see later, the delicacy and accuracy of this method is fully justified, it is somewhat surprising that it did not receive more extensive application. One serious difficulty stood in the way, namely, the technic of the estimation.

The next step depended on the discoveries of Haldane and Priestley[2] that the percentage of CO_2 in the alveolar air of normal individuals at atmospheric pressure is remarkably constant, and of Krogh that the amount of free CO_2 in the arterial blood is very nearly the same as that in the alveolar air. These facts led Haldane and his collaborators to formulate the hypothesis that the alveolar CO_2 must be proportional to the relative amounts of carbonic and of other (fixed) acids in the blood, and that when the latter are increased there must be a compensatory decrease in the former, provided the control of the respiratory function is normal. The first application of this principle on pathologic acidosis was made by Beddard, Pembrey and Spriggs,[3] who examined the alveolar CO_2 in diabetic patients, with the result that a very pronounced diminution was found whenever the comatous condition existed or was threatened. The rationale of this method and its limitations we shall discuss later; for the present it may be stated that the alveolar CO_2 may also be depressed in other diseases, particularly nephritis, as well as in normal persons whenever acids accumulate in the organism as a result of deficient oxidation in the tissues (Haldane, etc.).

Clearly, therefore, the term acidosis must not be confined to cases of diabetic coma. On the other hand the common appearance of acidosis in this

disease, coupled with the fact that in it the acids are of a type that is different from that found in nephritis, or during partial asphyxiation, makes it important that some term should be set aside to designate the diabetic condition. Since the acids are closely related to ketones (acetones) in chemical structure, the term "ketosis" has been suggested, and is gradually coming into general use. Ketosis, therefore, means the form of acidosis that is caused by the appearance of ketonic acids in the organism. Other forms of acidosis have not as yet been dignified by special names.

The remarkably rapid development of our knowledge of this subject during recent years, coupled with its dependence upon certain fundamental principles of physical chemistry, has made it very difficult for those of the medical profession who have been out of college for several years to appreciate the full significance and value of closely observing the neutrality regulation in the animal body in order that incipient states of acidosis may be detected. I will therefore attempt to review very briefly these fundamental principles, and to explain the various tests by which alterations in the reaction of fluids in general may be detected.

In the first place we must clearly understand what is meant by an acid such as HCl, and an alkali, or base, such as NaOH. When the molecule of either of these chemicals is dissolved in water it splits, or dissociates, into two portions called ions; in the case of HCl, for example, ions of H and Cl are formed, and in the case of NaOH, Na and OH. Moreover, each of the ions carries an electric charge, and this is always of opposite sign for the two ions composing the molecule. The sign of the electric charge for the H ion and all metals is positive, and that of Cl and all acid groups is negative. Since, as is well known, unlike electricities attract each other, this means that the positive ions like H would be attracted towards the negative pole or cathode of a pair of electrical terminals, between which a current is passing, placed in the solution. They are, therefore, called cations, and for the same reason the negative ions are called anions. To indicate these electrical charges, a dot is used for positive, and a dash for negative, thus, $H^{\cdot}$ and Cl'.

But what, it may be asked, have these principles of electrolysis to do with the question of reaction? The answer is that it is the presence of free $H^{\cdot}$ ions that determines the acidity of a solution. If we examine the formula of all known acids it will be seen that they have hydrogen in some displaceable or dissociable form in the molecule, and, furthermore, if we measure the acidity, as judged by the common standards of this property, such as the ability to dissolve metals, the acid taste, the power of inverting sugars and starches, and so forth, we shall find that it runs parallel with the dissociability of the H ion from the rest of the acid molecule. The $H^{\cdot}$ ions present in a free state in the solution must, therefore, be an accurate measure of its acidity. This leads us to expect that the presence of free OH' ions must be a measure of alkalinity, since we know that when an acid and a base are brought together, the one neutralizes the other by a reaction which consists essentially in the combination $H^{\cdot}$ and OH' ions to form H_2O. This removes the ions from the free

state and so locks them up, because molecules of water practically do not dissociate.

We have learned two fundamental principles, namely, that the standard of perfect neutrality must be where H· and OH′ ions exactly balance each other, and that the true acidity of a solution will be represented by the excess of free H· ions over OH′ ions, that is, by the H·-ion concentration (C_H). But we can go further, for not only may the acidity be expressed in terms of C_H, but so also may the alkalinity. Why should this be? It is clear that the most strictly neutral solution must be pure water, in which H· and OH′ ions are exactly counterbalanced. Nearly all of the H· and OH′ are combined in an undissociated molecule H_2O, but not all, for even in the purest water a slight degree of dissociation occurs, giving us therefore H· and OH′ ions. When the concentrations of the two ions are multiplied together the product is 1.2×10^{-14}, which means that there are 1.2 gram molecules of hydrogen (or its equivalent) present in, 10,000,000,000,000 liters. Since the concentrations of H· and OH′ ions are equal, the H·ion must therefore, be 1.2×10^{-7}, which means that this ion is present so as to form a .000,000,12 N solution is 1.2 gm. H· in 10,000,000 liters.

When some acid is added to the water the con. of H·ions, of course, rises, but, and this is the fundamental point to bear in mind, the con. of OH′ ions correspondingly falls so that, as in pure water, *the product of the two concentrations is again* 1.2×10^{-14}. However acid or alkaline a solution may be, the product of the concentrations of the H· and OH′ ions is always the same. Clearly then *we may express the reaction even of alkaline solutions in terms of the H ion concentration.* Whenever this is greater than 1.2×10^{-7}, the reaction is acid, but when it is less than 1.2×10^{-7}, the reaction is alkaline.* It is usual to abbreviate the expression hydrogen-ion concentration into C_H.†

These considerations lead us to seek for methods by which C_H may be measured. These are two in number, namely, the electrical and colorimetric. Concerning the former, suffice it to say that it consists in measuring the voltage or electric force set up in a battery of which one electrode is pure hydrogen gas in intimate contact with the solution whose C_H we desire to measure, and the other electrode is one of known voltage, such as the so-called calomel electrode. The rate of diffusion between the free H· ions in the solution and the H which constitutes the one electrode, is naturally dependent upon the concentration of free H· ions, and it is on this that the development of electric force depends at this electrode. Consequently since everything else is constant in the battery, the total electromotive force must be proportional to the C_H of the unknown solution.

The colorimetric method is much simpler, but not so delicate. It depends on the fact that certain indicators change in tint in proportion to C_H. In

*The exact value of 1.2 varies with temperature. When C_H becomes greater than that of neutrality the number 1.2 becomes greater, and if the change be beyond 10 the characteristic (-7) becomes less.

†For convenience of expression it is usual to designate the H-ion concentration by P_H instead of C_H. P_H is obtained by finding the logarithm of the number of gram molecules of H (i.e., 1.2 in the above example), and subtracting this from the characteristic (i.e.,-7 in the above example). Since the minus sign is understood P_H increases in magnitude as the H-ion concentration (expressed by C_H) decreases. In the present article C_H is used because its use is less confusing in a general discussion of the acidosis problem.

titrating solutions, such as the stomach contents, for the degree of acidity, the impression is apt to be formed that the tint changes suddenly at the neutral point. This is not the case however, for if the titration be done by very small additions of acid or alkali about the neutral point, it will be found that there is a fine gradation from the typical acid color to the typical alkaline color.

The exact C_H at which indicators change in tint varies with the indicator. Thus phenolphthalein, which is used in certain titrations of stomach contents, changes in tint at a much lower C_H than methyl orange or litmus, and with none of these indicators does the point of change occur at a C_H of $1.2 \cdot 10^{-7}$, so that they are unsuitable for measurement of the C_H of solutions that are nearly neutral. Fortunately, however, such indicators exist, the best known of which are sulphophenolphthalein, rosolic acid, and neutral red. If therefore we take a series of solutions having slightly variable, but known, C_H about the neutral point, and add to each a drop of one of the latter indicators, we shall obtain a series of graded tints, and the tint will be proportional to the C_H. The preparation of the standard solutions is not a difficult matter, provided ordinary precautions are taken. Mixtures of acid and basic phosphates in varying proportions are most practical.[4] The resulting mixtures should be measured electrometrically for accurate work. In order to determine the C_H of an unknown solution, some of it is placed in a hand glass test tube and an amount of suitable indicator is added so that the proportion of indicator to solution is the same as in the standards. The tint of the standards with which the tint of the unknown matches is then ascertained and this gives C_H. When the colorimetric method is employed for blood, it is of course necessary to get rid of the blood pigment and also of the proteins since these interfere with the reaction. This is accomplished by placing a few cubic centimeters of blood in a dialyser in the shape of a collodion tube, and suspending this in neutral physiologic saline. The saline soon assumes the same C_H as the blood, and this can be measured by the above described method.

When C_H of the blood is measured by one or other of these methods the significant fact is revealed that it is practically always the same, and is not far removed from that of pure water; at 38° C. C_H equals 0.4×10^{-7}. Even in severe cases of diabetic ketosis, an increase in C_H becomes perceptible only in the final stages of the condition. Clearly, therefore, even the slightest increase in C_H is incompatible with life, and C_H of the blood must be considered as a physiologic constant. It is greatly more so than body temperature or blood pressure, so that its measurement can be of little practical value in the clinic, and the question arises as to how the early stages of changes that might ultimately end in death from an increase in C_H may be detected. To answer this question we must study *the nature of the mechanism by which neutrality is maintained in the organism;* in other words why it should be the case that large quantities of acid can be produced in the body, as in diabetes, without any perceptible change in C_H.

When even a trace of acid is added to water or an isotonic solution of sodium chloride, a very pronounced change occurs in C_H, but it requires ever so much more acid to produce any perceptible change in the case of blood. For

example, using the colorimetric method let us observe the change in tint produced by adding a drop of weak HCl to water containing sulphophenolphthalein and then see how much of the same acid must be added to bring about a similar change of tint in a dialysate of blood. It takes very much more. Clearly the blood contains something which as it were soaks up the added H ions. This has been called the *buffer action* of blood, or better still, the *tampon action.* The question is, to what is this buffer action due? A clue is furnished by using solutions of phosphates. For example, if we take a solution containing alkaline and acid phosphates in such proportion that C_H is the same as that of blood, and then add acid, we shall find that ever so much more has to be added than is the case of water. The same is true of solutions of bicarbonate.

This property of phosphate has been carefully studied by L. J. Henderson,[5] to whose brilliant researches we are primarily indebted for the recent development of our knowledge in this whole question. Henderson found that weak acids like acid phosphate and carbonic acid possess the property of holding the H-ion concentration nearly constant, i.e., of acting as buffers, when they are present in solutions containing an excess of their salts. Now, in so far as the blood plasma is concerned, it is not phosphates, but rather bicarbonates to which the buffer action must be due, and as a matter of fact it has been found that C_H is directly proportional to the ratio existing between CO_2 in solution as H_2CO_3 and sodium bicarbonate $NaHCO_3$ multiplied by a constant; or, expressed in chemical notation, C_H = the molecular ratio $\frac{H_2CO_3}{NaHCO_3}$. This ratio is $\frac{1}{20}$, and we may define acidosis as any condition in which the proportion between H_2CO_3 and $NaHCO_3$ becomes greater than 1:20. It must be clearly understood that this applies only to isolated plasma, for when whole blood is used, other substances come into play in maintaining neutrality; the phosphates, for example, though practically absent from plasma, are nevertheless present in the corpuscles through the envelopes of which diffusion more or less readily occurs, so that they serve as a reserve buffer. Proteins also may serve either as weak acids or alkalies, and therefore neutralize quite decided quantities of added acid or alkalies. But for practical purposes we may regard the buffer agency as being the ratio $\frac{H_2CO_3}{NaHCO_3}$ and the problem of finding practical means for the detection of threatened acidosis now narrows itself down to a study of the behavior of this ratio.

Suppose that some fixed acid were added to a buffer solution containing bicarbonate. It would react with $NaHCO_3$ to form a neutral salt of the acid, and consequently set free some H_2CO_3, that is, it would diminish the denominator but increase the numerator of the equation $\frac{1}{20}$. The increase in C_H would not be proportional to that of the added acid, on account of the buffer mechanism (because H_2CO_3 does not dissociate well) but it would nevertheless increase somewhat just as any kind of buffer takes up most, but not all, of a force applied to it. This indicates that if the foreign acid were being added continuously, as would be more or less the case in pathologic acidosis, C_H would rise in spite of the buffer unless some method existed for decreasing the numera-

tor of the equation, i.e., getting rid of H_2CO_3. This is one of the functions of the lungs, the CO_2 excretion through which must therefore, be considered as a necessary part of the neutrality mechanism of the body. The CO_2 is got rid of until the ratio $\frac{H_2CO_3}{NaHCO_3}$ comes back to its old level of $\frac{1}{20}$. But now, much of the $NaHCO_3$ having been used up to combine with the foreign acid, the actual amount present is much less than before. This means that the H_2CO_3 must also be less, that is, the CO_2 in a free state in the blood plasma. Now, since as we have seen, the pulmonary epithelium permits the free CO_2 of the blood to diffuse readily through it, it follows *that the percentage of CO_2 in the alveolar air must be a measure of the available $NaHCO_3$ in the blood.* To repeat, for this is the fundamental conception of the whole acidosis problem, since C_H remains constant in the blood the ratio $\frac{H_2CO_3}{NaHCO_3}$ must also remain at its normal value of $\frac{1}{20}$, and, therefore, if $NaHCO_3$ declines, H_2CO_3 must decline proportionately, and since this diffuses as CO_2 into the alveolar air, the percentage of this gas in the latter must be proportional to the degree to which foreign acid can be added to the blood without perceptibly changing C_H, in other words it must be proportional to the reserve alkalinity.

One other factor must clearly come into play to permit of the smooth operation of the above mechanism, namely, the rate of pulmonary ventilation must be adapted to the amount of CO_2 that has to be eliminated. This adaptation depends on the respiratory center, the activity of which is preeminently dependent upon the acid base equilibrium in the blood.

It is commonly taught that the thing that really stimulates the respiratory center is not the CO_2 itself, but the slight increase in C_H which, as explained above, inevitably occurs, in spite of the buffer action. This is, however, probably an incorrect view, for R. W. Scott,[6] working in my laboratory, has found that CO_2 itself can excite the center quite independently of the H-ion concentration of the blood. Thus Scott found after injecting sodium carbonate into decerebrate cats until the C_H was very decidedly lowered, that a subsequent increase in the free CO_2 of the blood excited respiration almost to the same degree as would have been the case when the C_H of the blood was the normal, and furthermore, that when this excitement occurred, the blood was still markedly alkaline.

So long then as the center responds immediately to the slight excess of free CO_2 this is got rid of, and the normal ratio between H_2CO_3 and $NaHCO_3$ is reestablished. If the sensitivity of the center should be below par, however, then CO_2 might accumulate in the body and C_H consequently rise. As a matter of fact, even in health, it seems to be established that the excitability of the center may vary, as for example, in relationship to the amount of oxygen in the blood supplying it, and in disease there can be no doubt that such variations in excitability occur. And since we know that the activities of this center are also greatly affected by nerve stimuli, arriving at it along afferent nerves, it is to be expected that it may be keyed up or down in excitability by the state of the nervous system in general. In conditions of nervous excitement and anxiety,

for example, its sensitivity is increased and moderate doses of narcotic drugs, such as morphine, are well known to depress it.

But even were the sensitivity of the center maintained at a constant level, the alveolar-CO_2 would correspond with that of the arterial blood only provided that the exchange of CO_2 across the alveolar epithelium was strictly normal. And when we bear in mind that the proper excretion of the CO_2 in the lungs is dependent upon an accurate adjustment between the heart's action and the rate of CO_2 production in the organism, we see how the mechanism might readily become upset.

Technical difficulties have also to be overcome in the collecting of the alveolar air, for it is now well established that the original method of Haldane and Priestley is approximately accurate only when it is carried out under strictly controlled conditions—so strict that they can not be practiced in the clinic—and even then, as R. G. Pearce, Carter, Krogh, Siebeck and others[7] have shown, we can not be certain of the results. At best, therefore, *the alveolar CO_2 can serve as an accurate index of the acid base equilibrium of the blood only under certain controlled conditions.*

These facts have prompted the most recent observers (Morawitz and Walker[8] and later Van Slyke and Cullen[9]) to return to blood examination for the detection of impending acidosis. The question is what readily measurable property of the blood may we employ? If we return for a moment to the equation $\frac{H_2CO_3}{NaHCO_2} = \frac{1}{20}$ we shall see that when foreign acids combine with the Na of the bicarbonate, this will become replaced by the salts that are formed, such as NaCl, and these will be incapable of acting as buffers. The amount of $NaHCO_3$ present in the blood must, therefore, be a measure of its power to take up such acids without serious disturbance in C_H, which has led Van Slyke to define acidosis as "a condition in which the concentration of bicarbonate in the blood is reduced below the normal level." According to this definition, acidosis is not necessarily an increase in the actual C_H of the blood, or even it is a disturbance in the normal ratio $\frac{H_2CO_3}{NaCO} = \frac{1}{20}$ but is a lowering of the absolute values forming the numerator and denominator of the equation. In brief, it is a lowering of the ability of the blood to take up fixed acid without disturbance in the ratio, a decrease in the reserve alkalinity. The definition is, however, somewhat unfortunate, since it does not include cases in which there is an actual increase in the ratio as a result of the addition of H_2CO_3 to the blood, and such conditions may develop as a result of asphyxia, which, of course, is a common enough cause of acidosis in the broader sense. Moreover, in asphyxial acidosis it may quite well be the case that the $NaHCO_3$ instead of being diminished, is actually increased in the attempt to bring the ratio back to its normal value. When CO_2 is added to blood, for example, it has been shown that the alkali content of the plasma relatively increases, partly because of the migration of K and Na out of the corpuscles into the plasma, and partly because HCl goes in the opposite direction. There can be no doubt, however, that deficiency in bicarbonate is an im-

portant thing to measure as a gauge of the ability of the blood plasma to hold C_H constant when foreign acids are added to it.

In its newer form this test differs considerably from the form in which it was originally employed by Walter (see p. 316), for instead of measuring the CO_2 content of a sample of blood immediately after removal, this is first of all exposed outside the body to an atmosphere containing a known, fixed, percentage of CO_2 until all of the available alkali has become combined with this gas. This procedure removes the most serious objection to the old technic, namely, that the amount of CO_2 in the venous blood,—and that alone is of course available for use in man,—must be very largely dependent upon the rate of oxidation in the tissues, and upon the velocity of movement of blood through the capillaries which drain into the vein. In experimental work on animals, however, the CO_2 actually present in arterial blood remains as the most practical indicator of the buffer action of the blood. Being restricted in man to the use of venous blood, the questions which remain to be answered are: 1. What pressure of CO_2 should be chosen with which to saturate the blood?* 2. Should whole blood or plasma or serum be employed? With regard to the CO_2 pressure, there are two alternatives: we may use either the pressure to which the blood is actually exposed in the organism, the *intra vitam* pressure we may call it, or an arbitrarily fixed pressure. The *intra vitam* pressure of CO_2 can be determined by analysis of the alveolar air, but this, of course, complicates the technic and gives us no more accurate an estimate of the available alkali than when we use the same pressure for all samples.

Concerning the question as to whether whole blood or serum should be used, there can be little doubt that it should be the former. The objection to the use of serum or plasma depends on the fact, as we have seen, that a part of the alkaline reserve resides, not in the fluid menstruum of the blood, but in the corpuscles, and even beyond this, in the tissue cells. It has been known for some time, for example, that when CO_2 is bubbled through whole blood, the alkali content of the plasma decidedly increases, as judged by titration, and when the blood is in contact with the tissue cells it is quite likely that when excess of acid appears in it, there may be a considerable transference, not only of more alkali from the cells into the blood, but also of CO_2 in the opposite direction, (into the cells including the red blood corpuscles) in which it may become combined with alkaline phosphates by such reactions as are illustrated in the equation:

$$Na_2HPO_4 + H_2CO_3 = NaH_2PO_4 + NaHCO_3.$$

It should be remarked that Van Slyke recognizes these possibilities, but nevertheless, he believes that for practical purposes it is allowable to employ venous blood, and to saturate its plasma with CO_2 at a definite partial pressure. The results which he and other workers using his method have employed would certainly appear to justify his claim at least for the detection of cases in which the alkaline reserve is decidedly reduced, but it should not be lost sight of that a strict observance of the principles which we have attempted to explain might

*It may be pointed out, for the sake of those who are not familiar with the work in this field, that the pressure of a gas in a mixture of gases is proportional to its percentage amount; thus 6 per cent CO_2 will give 45.6 mm. Hg pressure at a barometric pressure of 760, for 100 : 760 : : c : x.

make the gauging of the alkaline reserve a still more valuable criterion of disturbances in the acid base equilibrium in the organism.

To sum up, it may be said that determination of the ability of blood to absorb CO_2 is probably the most practical method for measuring the acid neutralizing power; it measures the degree to which the acid buffer can functionate or, as some call it, the alkaline reserve. This high estimate of its value holds good, however, only when the whole blood is taken, but *even then we do not necessarily measure the total reserve of the body*. These reserves are, first, the alkalies of the plasma, second, the alkalies of the corpuscles, third, the proteins of the blood, and the last reserves are probably the alkalies and the proteins of the tissue cells. Now it is clear that there can be no test-tube method by which the magnitude of all of these defensive agencies could be measured; at best we can only measure the first three of them, namely, the reserve power resident in the blood itself. Christiansen, Haldane and Douglas[10] and contemporaneously Morawitz and Walker,[8] have recommended this method, and it is only more recently that Van Slyke, in order to simplify the technic, has advocated the employment of blood plasma (oxalated) alone. Let us consider for a moment, therefore, whether the Van Slyke technic is really much simpler than that employed by Haldane. In the method used by these observers a cubic centimeter, or so, of defibrinated blood is exposed at body temperature for twenty minutes, in an air-tight vessel, to an atmosphere containing a known amount of CO_2. A measured sample is then removed to the gas analysis apparatus of Haldane-Barcroft, and the CO_2 is determined by decomposing the carbonates with strong acid, after getting rid of the oxygen by shaking with ferricyanide solution. The procedure is comparatively simple, and can easily be done with a little practice in the wards.

In Van Slyke's method, the oxalated plasma, separated by rapid centrifuging, is exposed to an atmosphere of expired air in a tonometer, and the plasma then transferred to a gas analysis apparatus, that is certainly no simpler in manipulation than that of Haldane and Barcroft (see Vol. II, p. 55 of this Journal), and which moreover suffers from the disadvantages: first, that the slightest leakages around the stopcock involves a very serious error because of the vacuum which is established in the apparatus at a certain stage of the manipulation, and secondly, that it requires the use of mercury which becomes fouled with the mixture of plasma and acid during the analysis.

Taking into consideration the theoretic objections to the use of plasma or serum in place of blood, and also the doubtful advantage to be gained by using the Van Slyke apparatus, at least by those who are not practiced in the use of gas analysis methods in general, there is no very evident reason why the Van Slyke procedure should be followed in preference to the earlier, really simpler methods of Haldane, etc., and of Morawitz and Walker.

It has been pointed out above that the sensitivity of the respiratory center towards the C_H, or more probably the free CO_2, of the blood is apparently much greater than that of any other center or mechanism in the animal body, and that it is on account of this sensitiveness that the free CO_2 of the blood is immediately got rid of from the body by increased pulmonary ventilation, whenever there is tendency for the C_H to rise above the normal level. As the free CO_2 is got rid of,

the bicarbonate decomposes, because of the presence of other acid groups in the blood, e.g., protein, etc., and the amount that is left indicates the remaining ability of the blood to withstand further addition of foreign acid. Clearly, therefore, the important thing to measure in order that we may be enabled to diagnose the incipient stages of acidosis is the alkaline reserve, and but one question remains to be considered, namely, whether arterial or venous blood should be employed. For various reasons arterial blood is preferable. In the first place the percentage of CO_2 actually present in it is proportional to the alkaline reserve, so that it is unnecessary to expose the blood to an atmosphere containing CO_2 before measuring the CO_2 content, and in the second place, it represents the mixed blood of the body, and not that of only one locality, as is the case with blood removed from a peripheral vein. But in clinical practice venous blood only is available. If this is collected with the precaution that the muscles in the corresponding area have been at rest for some time it appears that there is practically no difference between the alkaline reserve of arterial and venous blood, but if there has been any muscular contraction, the venous blood will have a lower reserve than the arterial, because of the lactic acid thrown into it by the contraction. But even when we take the precaution of avoiding muscular action, it is probable that there is not a strict parallelism between the buffer action of arterial and venous blood as in cases in which the demands on the alkaline reserves are such that those of the tissues are being called on as well as those of the blood itself. The experiment of Van Slyke,[9a] in which he compared actual CO_2-containing powers of arterial and venous blood removed from anesthetized dogs, and found them to be very nearly the same, does not throw any light on this phase of the problem.

The chief criticism against the use of the CO_2 carrying power of blood or blood plasma, is therefore, that it tells little if anything concerning the acid-absorbing powers of the tissues. Is there not, therefore, some test of the acid buffer which can be applied to the intact animal? One such we have already considered, namely, the percentage of CO_2 in alveolar air, and we have seen that it is not entirely satisfactory partly because of the technical difficulties in the collection of the sample of air for analysis, and partly because of possible variations in the sensitivity of the respiratory center. In order to place an estimate on the relative value of these methods comparisons have been made between the CO_2 tension of the alveolar air and the CO_2 absorbing power of the blood. This has been done both in normal and pathologic subjects. In normal subjects the comparisons have been made under conditions, such as the taking of food and during muscular exercise, in which slight alterations in the acid-base equilibrium are known to occur. Van Slyke, Stillman and Cullen[9b] found that the ratio $\frac{\text{plasma } CO_2}{\text{mm. alveolar } CO_2}$ varies from 1.27 to 1.80 in different resting individuals, there being apparently a characteristic ratio for each individual, and that the taking of food invariably raises the alveolar CO_2-combining power. This would seem to indicate that it must be the excitability of the respiratory center rather than the acid base equilibrium that becomes altered so as to cause variations in alveolar CO_2. The same authors, in conjunction with Fitz, working on the above

relationship in patients suffering from diabetes and nephritis, found that in the former disease, under treatment, the alveolar CO_2 tension is often much too low in comparison with the blood bicarbonate. On the other hand the tension is always low in these cases when the bicarbonate content of the blood is low. In nephritis, however, the tension of alveolar CO_2 may be high although the blood CO_2 is low. Peters[12] has also examined these relationships, and has met with many instances where satisfactory parallelism did not exist. One serious criticism of this work is, however, that the method of Fridericia was employed for collecting the alveolar air.

Christiansen, Douglas and Haldane[10] did not find a relation to exist between the CO_2 absorbing power of the blood and the normal resting alveolar CO_2 in different healthy individuals, but after severe muscular exercise, the interesting discovery was made that marked reductions occurred both in the CO_2 absorbing power of the blood, and in the alveolar air, and they suggested "that corresponding differences will probably be discovered under various pathologic or compensatory conditions for acidosis."

In all these comparisons it is with the arterial CO_2 tension that the alveolar CO_2 is believed to run parallel, the air samples being removed from the alveoli under conditions which mean that the gaseous equilibrium must be between alveolar air and arterial blood. The question therefore arises whether more exact parallelism between alveolar CO_2 and blood CO_2 might not be obtained if the venous CO_2 tension were taken instead of the arterial. As shown by Christiansen, Douglas and Haldane, and later by Y. Henderson[11] and R. G. Pearce,[13] the alveolar venous CO_2 tension can be measured by the comparatively simple expedient of causing the patient to inspire an atmosphere containing a percentage of CO_2 above that which corresponds to the free CO_2 of venous blood, and then removing successive samples of the expiration which follows, and analysing each for CO_2. The portions expired at first will contain approximately the same percentage of CO_2 as that in the inspired air, but the percentages will progressively decline in the succeeding portions until at last they become constant at a level which must correspond to the venous CO_2 tension. In the method of Plesch for the collection of alveolar air, in which the person takes several breaths in and out of a rubber bag, the CO_2 percentage of the air in the bag must approximate more closely the CO_2 tension of the venous blood than that of the arterial. It is certainly important that the possibility of a parallelism between alveolar venous CO_2 tension and CO_2 combining power of the whole blood should be thoroughly investigated. On *a priori* grounds the parallelism is likely to be a much closer one than when the comparison is made between alveolar (arterial) CO_2 tension and CO_2 combining power of blood plasma.

By an application of these principles, therefore, it does not appear that there is a simple, thoroughly reliable method by which the buffer action of the body as a whole can be measured. An entirely different plan of attacking the problem must be thought of, namely, to observe the acid excretion by way of the urine.

When we were considering the general nature of the chemical reactions between the salts of the blood and added acid we saw that besides free CO_2 there

would have to be eliminated from the body a considerable amount of acid salts, or of free acids. In this connection the body must be considered as a whole, and when foreign acid is added a corresponding amount must ultimately be eliminated, if the normal acid-base equilibrium is to be reestablished, even although a sudden change in C_H is avoided by the buffer action. Most of this excess of acid, as we have seen, is eliminated by the lungs as CO_2, but the remainder has to be got rid of by other pathways of excretion, particularly the kidneys. The excretion of the acid excess by this pathway occurs in three forms: *first* as acid salts, for example by conversion of Na_2HPO_4 into NaH_2PO_4, *second* as salts of ammonia and *thirdly* as free acid. Concerning the second of these, under normal conditions ammonia is a product of metabolism split off during the break down of amino acids, and then rendered innoxious, by combining with carbonic acid to form ammonium carbonate which is converted into urea, a strictly neutral substance. When excess of acids must be neutralized, however, some of the ammonia instead of combining with CO_2, may be diverted to neutralize the excess, this being particularly the case when ketonic acids appear, as in diabetes. The ammonia excretion itself is, however, no reliable indicator of the amount of free acid in the body, because there are other conditions such as derangement of the hepatic function which may influence it. In the toxic states of pregnancy, for example a large excretion of ammonia may occur without any indication of an acidosis. With regard to the acid which may be excreted in a free state, this occurs, for example, with β-oxybutyric acid, which is so weak in its acid properties, that 45 per cent of it may be excreted in this form.

With such a multiplicity of forms of excretion it is clear that *the only satisfactory method for measuring the acid excretion by the kidney must be one in which all of the above forms of excretion are included.* To measure the amount of free acids and acid salts the theoretically correct method would be to titrate the urine with standard alkali until its C_H, which is normally on the acid side of neutrality, was brought to the same level as that of blood. This can be done by using sulphophenolphthalein which, it will be remembered, changes tint at about the C_H of blood. For practical purposes, however, it has been found more convenient to use phenolphthalein, the neutral point of which is such that when urine just reacts neutral to it, the CO_2 combining power of the blood plasma as tested by Van Slyke's method, is at its maximum by 80 vols. per cent, and the ammonia excretion is zero. By titrating a sample of urine after adding neutral oxalate to it,—in order to precipitate substances which interfere with the sharpness of the end point—with $N/_{10}$ NaOH to the neutral point of phenolphthalein we measure the total of free acids and acid salts, and if we now add to this the amount of ammonia in the same urine, (readily measured by Folin's new permutit method), we obtain the *total urinary acid excretion.* It is said that a definite relationship exists between the CO_2 combining power of the plasma and the total acid excretion, a relationship, however, which can be made clear only when a rather arbitrary equation like that of Ambard is employed. It remains to be seen of what value the determination of this ratio may be in clinical diagnosis.

There remains possible another method for gauging the alkaline reserve, namely, to see *how much alkali can be added to the organism without causing the*

urine to assume an alkaline reaction. When the alkaline reserve of the body is about normal, it is clear that very little alkali will suffice to have this effect. As a matter of fact, it has been found by Sellards[14] and by Palmer and Henderson[15] that only 5 grams a day, can be taken without making the urine alkaline. When the alkaline reserve is seriously depleted, however, large quantities of bicarbonate, even as much as 100 grams a day can be taken without making the urine alkaline. This test has been found of particular value in the diagnosis of acidosis accompanying certain forms of renal disease (chronic interstitial nephritis), which raises the question as to whether the retention may not be due to faulty elimination of the bicarbonate rather than to its retention in order that a deficient alkaline reserve may be corrected. It has not been a very simple matter to entirely disprove this possible explanation, and experiments of a variety of types have had to be devised in connection with the problem. One of them consists in determining the effect of a second dose of bicarbonate administered to an acidosis patient to whom a sufficient amount had previously been given to render the urine just alkaline. It has been found that a few grams now suffice, indicating, apparently, that the alkaline reserve must have been restored to its normal level. Even to this experiment the objection can be raised, however, that the large doses were retained because the threshold of the kidney for the excretion of bicarbonate was a very high one, and that the second, smaller administration just sufficed to overstep this threshold.

Sellards' careful work with this method seems quite clearly to establish its value, however, and for practical purposes *it is no doubt the best test of acidosis at present available in routine clinical work.* It has the important advantage, furthermore, of being simple and of requiring no elaborate apparatus.

Finally it may be advantageous to classify the possible causes which might lead to a want of stability in the C_H of the blood; that is, to threatened acidosis or alkalosis, not of acidosis in the narrow sense implied in Van Slyke's definition, but in the broader sense of any disturbance in the acid-base equilibrium.

In general a tendency to acidosis might be due to an increase in the numerator or decrease in the denominator of the molecular equation $\frac{H_2CO_3}{NaHCO_3} = \frac{1}{20}$, or to a proportionate decrease in both. In the latter case, there would be no actual change in C_H, but the alkaline buffer would be depleted so that the change would very readily set in when foreign acids were added. Furthermore, it should be understood that $NaHCO_3$ only stands as a symbol for all substances that might serve as alkaline reserves, for although this salt is no doubt the most important of these, the alkaline phosphates of the corpuscles, and the protein of the blood and tissues must also be considered. A tendency to alkalosis—which is no doubt extremely rare as a pathologic condition—would be due to changes of a reverse character. A theoretic classification of the conditions which might cause these changes is given:

Increase of C_H.

Addition or accumulation of acid	Accumulation of CO_2 (asphyxial conditions).
	Incomplete oxidation of carbohydrate (lactic and in muscular exercise).
	Defective oxidation of fat (ketosis).
	Renal insufficiency (nephritis).
	Decomposition of protein (as in acidosis of fever).
	Intestinal fermentation.
	Administration of acid (experimental).
Decrease of base	Diarrhea and hemorrhage, respectively (may explain acidosis in cholera and in certain forms of shock).

Decrease in C_H.

Addition or accumulation of base	Ammonia (faulty metabolism of urea).
	Intestinal putrefaction (infantile conditions).
	Administration of alkalies (experimental).
Removal of acids	Excretion of CO_2 (excessive pulmonary ventilation, as in faulty ether administration).
	Excretion of acid urine.

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THE EPIDEMIC OF INFLUENZA AT CAMP DEVENS, MASS.*

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THE epidemic of influenza and pneumonia which attacked Camp Devens was a part of the pandemic which swept across the United States in the late summer and early fall of 1918. Camp Devens was the first of the cantonments to be affected, and since no warning had been given, and no data regarding treatment or prophylaxis had been promulgated, the camp authorities were unembarrassed and unassisted by precedents in the management of the epidemic.

The disease appeared in the camp, as far as can be seen, on the eighth of September. It reached its acme on the sixteenth, seventeeth and eighteenth of the month and then rapidly declined, almost completely vanishing about the middle of November. The first cases were observed in members of Company B, 42nd Infantry. On September 7 a case of epidemic meningitis had been sent to the Base Hospital from this company. On the following day a dozen other members of the same company had been sent to the hospital for observation for meningitis, but these twelve proved to be merely what was called at the time, "nasopharyngitis, acute, catarrhal." Subsequent developments showed that the nasopharyngitis of this period was in reality mild "Spanish influenza." A definite diagnosis of influenza was made on September 12. On September 9, five more suspicious cases were sent to the hospital from the same company, and so on, until by September 16, thirty-six members of the one company had received hospital attention. Meanwhile, however, similar cases were being observed and sent to the hospital from other regiments and organizations, a state of affairs that brought about a sudden change in the general sick rate as shown in Table I of hospital admissions. The figures in this table will indicate the sudden and enormous strain which was thrown upon the hospital.

Table I

Hospital Admissions

September 1	39	October 8	78
2	31	9	79
3	51	10	100
4	80	11	68
5	78	12	81
6	95	13	51
7	95	14	58
8	93	15	80
9	93	16	69
10	142	17	75
11	186	18	78
12	227	19	59
13	350	20	51
14	502	21	36

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TABLE I—(Cont'd)

HOSPITAL ADMISSIONS

September	15	705	October	22	87
	16	1189		23	66
	17	1056		24	74
	18	1176		25	70
	19	624		26	59
	20	778		27	48
	21	684		28	45
	22	443		29	86
	23	578		30	91
	24	505		31	83
	25	386	November	1	65
	26	239		2	50
	27	173		3	47
	28	117		4	31
	29	117		5	73
	30	74		6	62
October	1	126		7	50
	2	93		8	54
	3	94		9	50
	4	76		10	40
	5	76		11	29
	6	78		12	49
	7	50			

These early cases of "nasopharyngitis" were looked upon at first as examples of the mild epidemic disease which had attacked many of the cantonments during the spring of 1918. At that time very many soldiers were affected by what seemed to be severe but transient "colds" without coryza. With this disease there were no fatalities. It may be justifiable to surmise that the cause of the mild but extensive spring epidemic was an attenuated or avirulent form of the organism which has been responsible for the recent epidemic, and that it became more virulent in the course of repeated passages from host to host. However that may be, it was not immediately realized that we were dealing with such an exceedingly serious disease until the complicating pneumonias began to appear in steadily increasing numbers, and this was not until after the epidemic had gathered headway of considerable proportions. Table II shows the number of new cases of pneumonia reported by the Base Hospital:

In the first week of September the pneumonias were evidently on the increase but for that there seemed to be perfectly good meteorologic and racial reasons. Of the cases appearing during the first fourteen days of September, 44 were in negroes,—a little over 50 per cent. Of the 25 cases occurring during the first seven days of the month, 16 were in negroes. And then it became increasingly evident that the mass of the pneumonias were very definitely related to the influenza. The evidence for this was (1) the ever-increasing number of pneumonias in patients who had been admitted for influenza; (2) the number of men who, upon admission, had both "flu" and pneumonia; (3) the number of men who were discharged from the hospital convalescent from "flu" who were readmitted for pneumonia; (4) the type of pulmonary lesions, as found at autopsy; (5) the bacteriologic findings.

The disease was no respecter of persons except that it was more severe

Table II

Pneumonia Cases

September 1	4	October 8	17
2	1	9	4
3	4	10	7
4	2	11	7
5	2	12	4
6	0	13	9
7	12	14	1
8	7	15	17
9	7	16	5
10	6	17	3
11	8	18	8
12	7	19	3
13	9	20	5
14	18	21	3
15	17	22	3
16	17	23	5
17	26	24	3
18	43	25	5
19	38	26	5
20	87	27	6
21	118	28	6
22	176	29	3
23	215	30	5
24	342	31	7
25	309	November 1	13
26	221	2	5
27	79	3	4
28	106	4	1
29	47	5	6
30	111	6	3
October 1	74	7	2
2	31	8	4
3	28	9	2
4	16	10	1
5	13	11	2
6	10	12	2
7	4		

in those who were hard workers. Those who tried to "buck the game" and "stay with it" showed the highest mortality rates. So, the noncommissioned officers and the nurses suffered more severely than the commissioned officers and privates.

Table III

Comparative Mortalities

Commissioned Officers	
Average strength	1194
Total pneumonia cases	30
Annual morbidity rate per 1000	261
Deaths	8
Annual mortality rate per 1000	69
Case mortality	26.8%
Noncommissioned Officers	
Average strength	3493
Total pneumonia cases	70
Annual morbidity rate per 1000	208
Deaths	28
Annual mortality rate per 1000	83
Case mortality	40%

Nurses

Average strength	225
Total pneumonia cases	9
Annual morbidity rate per 1000	416
Deaths	3
Annual mortality rate per 1000	77
Case mortality	33.3%

White Enlisted Men

Average strength	41,321
Total pneumonia cases	2,261
Annual morbidity rate per 1000	568
Deaths	388
Annual mortality rate per 1000	145
Case mortality	26%

Black Enlisted Men

Average strength	3074
Total pneumonia cases	334
Annual morbidity rate per 1000	1130
Deaths	75
Annual mortality rate per 1000	253
Case mortality	22.5%

NOTE: The above figures are for the period of five weeks from August 28 to October 1, 1918. They cover the most active portion of the epidemic but are obviously incomplete. They are given only for comparison.

Although the first cases of influenza appeared suddenly in a single company of the 42nd Infantry, it was but a few days until practically every organization, large and small, in the camp was affected, as the following tables will show. The figures used are the rates per 1000, for the days indicated, of total sick,—in other words it is the noneffective rate that is given and not the isolated influenza rate. The noneffective rate is given, in spite of the slight inaccuracy in applying it to influenza, because it is felt that the number of "all other diseases" helps to balance the number of unreported influenzas, i. e., mild cases which despite every effort were overlooked and so failed to be shown on the returns. However that may be, the variation from the exact truth would be so small that the end results would be prejudiced not at all.

TABLE IV

ORGANIZATIONAL NONEFFECTIVE RATES

		Infantry				Mch. Gun Bns.			Engineers	Supp. Trn.	Trns. M. P.
		36	42	73	74	34	35	36			
Sept.	1	15	21	14	13	—	24	23	—	16	—
	2	15	21	14	13	—	23	21	—	11	—
	3	14	23	14	14	2	23	23	2	11	—
	4	14	25	15	14	2	27	24	2	11	—
	5	14	25	18	14	5	21	26	2	5	36
	6	14	30	18	15	5	21	23	5	5	35
	7	14	30	19	16	4	15	23	7	5	31
	8	14	28	19	17	4	16	21	11	5	31
	9	15	30	21	18	4	21	23	12	5	33
	10	16	32	21	18	4	30	21	13	2	30
	11	15	34	22	20	2	38	22	15	6	36
	12	15	37	27	24	6	49	35	17	26	41
	13	15	37	38	34	10	68	—	23	75	52

TABLE IV—(Cont'd)

ORGANIZATIONAL NONEFFECTIVE RATES

		Infantry				Mch. Gun Bns.			Engineers	Supp. Trn.	Trns. M. P.
		30	42	73	74	34	35	36			
Sept.	14	14	37	45	50	10	93	—	32	85	58
	15	15	39	67	62	10	123	35	50	101	118
	16	21	64	105	77	25	227	86	76	120	160
	17	35	106	157	106	85	285	109	173	110	210
	18	44	119	196	150	116	230	106	206	168	250
	19	52	141	244	164	126	236	121	182	189	225
	20	62	153	252	204	146	320	137	182	133	232
	21	70	163	241	206	150	190	140	174	130	236
	22	63	151	251	191	150	151	161	200	115	238
	23	75	160	259	226	176	204	170	241	133	241
	24	77	172	256	238	184	205	174	273	124	245
	25	78	156	243	243	176	190	158	278	111	239
	26	78	156	217	244	179	190	167	287	112	239
	27	76	154	196	262	184	158	165	286	97	243
	28	80	169	186	268	160	163	171	286	98	234
	29	76	146	177	202	146	147	156	275	95	233
	30	75	139	180	180	120	150	157	270	69	214
Oct.	1	72	134	171	168	125	136	144	271	71	209
	2	74	102	123	80	114	134	156	281	72	205
	3	74	96	120	78	108	87	156	290	69	202
	4	81	89	118	72	94	84	104	178	—	194
	5	78	85	120	70	92	82	123	157	75	193
	6	70	65	120	70	89	83	107	157	61	190
	7	63	71	110	68	79	98	100	122	61	202
	8	42	72	113	65	73	82	94	120	57	186
	9	42	72	104	63	73	86	88	—	57	157
	10	39	69	105	62	67	—	83	—	57	172
	11	38	67	105	61	59	79	75	105	57	170
	12	36	60	104	60	59	74	69	92	59	169

(N. B. All of the above organizations are parts of the 12th Division.)

TABLE V

ORGANIZATIONAL NONEFFECTIVE RATES

		Camp	Depot Brig.	13th Bn.	Dev. Bn.	Q.M.C.	A.R.D.	12th Division
Sept.	1	31	62	161	66	12	13	15
	2	32	60	153	67	14	15	16
	3	32	60	158	68	14	12	16
	4	32	58	160	66	13	10	17
	5	31	54	160	61	13	10	17
	6	31	53	160	61	12	10	19
	7	32	55	162	60	12	8	20
	8	32	56	166	62	12	8	19
	9	34	57	170	68	12	8	20
	10	33	61	175	68	11	8	21
	11	35	66	177	78	12	10	22
	12	38	70	176	88	12	12	24
	13	40	60	131	93	20	12	28
	14	48	72	139	110	25	12	34
	15	63	94	159	112	34	13	43
	16	86	113	181	115	34	13	65
	17	105	141	212	150	37	17	96
	18	125	161	250	158	43	26	125

TABLE V—(Cont'd)

ORGANIZATIONAL NONEFFECTIVE RATES

		Camp	Depot Brig.	13th Bn.	Dev. Bn.	Q.M.C.	A.R.D.	12th Division
Sept.	19	156	201	273	165	51	36	152
	20	179	231	282	166	55	58	172
	21	190	255	284	179	59	67	181
	22	196	260	290	177	56	55	166
	23	185	265	294	180	59	71	181
	24	189	268	300	190	60	76	193
	25	187	266	274	191	51	76	194
	26	185	224	240		49	76	190
	27	185	224	230		45	76	188
	28	185	202	167		40	74	187
	29	150	174	159		36	74	168
	30	127	136	161		35	72	157
Oct.	1	120	132	159		29	69	150
	2	116	127	158		30	56	140
	3	106	121	158		27	54	117
	4	103	117	158		29	50	113
	5	100	109	135		28	54	100
	6	92	106	117		29	52	95
	7	91	104	114		30	68	93
	8	87	102	114		35	68	85
	9	85	96	115		32	64	83
	10	81	91	115		27	59	79
	11	79	87	110		27	58	77
	12	79	90	106		29	49	71

(N. B. It is to be remembered that the camp includes all the organizations. The 13th Battalion, composed entirely of negro troops, and the Development Battalions are parts of the Depot Brigade. The Quartermaster's Corps and the Auxiliary Remount Depot are independent organizations. The Division includes all the other organizations tabulated.)

It will be seen from the foregoing figures that for a while the epidemic was slowly extending and that it finally acquired an almost explosive character, so that—

On September 17, 28.2% of the 35th M. G. Bn. was sick;
On September 19, 18.9% of the 212th Supply Train was sick;
On September 23, 26.0% of the 73rd Infantry was sick;
On September 24, 29.6% of the 13th Battalion was sick;
17.3% of the 42nd Infantry was sick;
18.0% of the 34th M. G. Bn. was sick;
17.4% of the 36th M. G. Bn. was sick;
13.3% of the A. R. D. was sick;
6.0% of the Q. M. C. was sick;
19.1% of the Dev. Bns. was sick;
24.6% of the Trains & M. P. was sick;
On September 25, 28.2% of the Field Signal Bn. was sick;
27.8% of the 212th Engineers was sick;
On September 26, 24.2% of the 74th Infantry was sick;
On September 28, 8.0% of the 36th Infantry was sick;

or, put in another way—

On September 22, 19.6% of the total camp personnel was sick;
On September 24, 19.4% of the 12th Division was sick;
26.8% of the strength of the Depot Brigade was on sick report.

The preceding figures give some idea of the rapidity of spread of the disease and of its extent in the camp. In all more than 30 per cent of the population was affected. Roughly speaking the rise of the curve occupied the interval between September 8 and September 17; the crest extended over the five days from September 17 to September 21. The fall was at first abrupt for seven to eight days and then more gradual extending over several weeks.

On	September	18,	6674	cases	had	been	reported.
"	"	19,	there	were	1184	new	cases.
"	"	20,	"	"	1543	"	"
"	"	21,	"	"	1179	"	"
"	"	22,	"	"	868	"	"
"	"	23,	"	"	616	"	"
"	"	24,	"	"	458	"	"
"	"	25,	"	"	271	"	"
"	"	26,	"	"	240	"	"
"	"	27,	"	"	153	"	"
"	"	28,	"	"	221	"	"
"	"	29,	"	"	107	"	"
"	"	30,	"	"	38	"	"

From September 30 on there were a few less cases each day or so, with occasional rises until the latter part of October and the first of November when they practically disappeared.

The epidemic persisted for a shorter period in the camp than it did in the surrounding cities, including Boston, because the population of the camp was more concentrated, and also because less was undertaken in the way of quarantine than in those centers. It was apparent that the disease was everywhere in the camp almost from the start and therefore the energies of the surgeons were expended upon treatment rather than upon other measures. Comparative studies indicate that the procedures were justified.

So far as is known there were no fatalities from uncomplicated influenza. In every fatal case but two a diagnosis of pneumonia was made, and in these two cases pure cultures of pneumococcus were obtained from the blood after death, so that it appears that they were cases of pneumococcus septicemia. In all, 2817 cases of pneumonia were reported in connection with the epidemic covering the period ending October 29, a figure which represents about 19 per cent of the total number of influenza cases reported during the period. Of these 787 died—a case mortality of 27.9 per cent and about 5.4 per cent of the influenza cases. The pneumonias were of two types—lobar and lobular (or broncho), the latter predominating in the white men, the former in the negroes. The characteristic cases in white men seems to have been a pseudolobar pneumonia, which accounts for the frequent clinical diagnosis of lobar pneumonia, while in the negroes the typical lesion was perfectly frank lobar consolidation. The latter seems to cause a lower mortality in the negroes than the former does in the whites, and so the difference in mortality in the two races is most readily explained.

Table VI shows the number of cases of pneumonia in the Base Hospital from day to day, and will serve to indicate the enormous burden thrust upon the personnel of that institution.

TABLE VI

PNEUMONIA CASES IN HOSPITAL AND THE PNEUMONIA RATE PER 1000 FOR EACH DAY

	Cases	Rate per 1000
September 1	127	2.9
2	128	3.0
3	130	3.0
4	128	2.9
5	129	2.8
6	142	3.1
7	152	3.3
8	159	3.5
9	164	3.6
10	168	3.6
11	174	3.8
12	176	3.8
13	185	4.0
14	146*	3.2
15	161	3.6
16	169	3.8
17	191	4.2
18	228	5.1
19	260	5.7
20	348	7.6
21	442	9.7
22	581	12.8
23	727	16.0
24	992	21.8
25	1215	26.7
26	1355	29.8
27	1902**	41.7
28	1933	42.5
29	1928	42.5
30	1993	44.2
October 1	2033	44.7

After October 1, the number of cases of pneumonia in hospital gradually decreased.

Pneumonia was already present in the camp when the epidemic of influenza appeared. It was widely scattered and was concentrated at but one point in the camp, i. e., in the 13th Battalion of the Depot Brigade, an organization composed entirely of negroes, most of them from Florida and the South. This battalion had just passed through an epidemic of pneumonia and was just about out of the woods when influenza attacked it. The result was striking. It seems certain that many of the blacks were harboring the pneumococci, which were only waiting a favorable opportunity to invade their hosts. Influenza furnished the required opportunity. Among the white men the conditions were somewhat different. In this group of the camp population there had been some cases of pneumonia but not many, and they were scattered, and the death rate was exceedingly low. Still, the pneumococci were evidently widespread in the camp and always a possible source of danger. It is interesting that under these circumstances the two races should suffer as they did, the white men

*At this time a considerable number of late convalescent pneumonias were discharged to make room for acute cases.

**This figure is due to taking up a number of previously unreported cases, unreported because of the clerical breakdown. They were not unrecognized or untreated cases.

from a lobular (influenzal?) type, and the negroes from a typical lobar type.

Pneumonia was a very early complication in a great many cases, though because of its early anatomic distribution it was frequently difficult to diagnose it by the usual methods of auscultation and percussion. Because of the fact that it usually develops centrally or near the hilus and progresses outward toward the pleura, it is apt to be overlooked. Nevertheless in very many cases sent to the hospital for influenza, pneumonic consolidation was discovered at the receiving station. For instance, in the records of seven days there were 139 cases diagnosed pneumonia on admission. At Camp Devens it was the rule to take no chances with influenza, and to send cases to the hospital as soon as possible. These cases justified the rule, if justification were needed, for it became very apparent that every case of influenza should be treated as a possible pneumonia until careful observation proved the contrary. The great variation in the time which might elapse in the development of these consolidations is shown in the following figures which were obtained early in the epidemic:

Diagnosis of pneumonia made	
On day of admission	1
On day after admission	41
Second day after admission	101
Third " " "	77
Fourth " " "	56
Fifth " " "	101
Sixth " " "	89
Seventh " " "	85
Eighth " " "	51
Ninth " " "	18
Tenth " " "	9
Eleventh " " "	1
Twelfth " " "	2

There seems to be very good and sufficient reasons for believing the influenza was introduced into Camp Devens from Boston. It is, however, impossible to decide whether the infection was carried into the camp by members of the civil community who had come to visit friends in the camp, or by soldiers who had been out of camp on leave. On Saturdays and Sundays there are enormous numbers of visitors to the camp, and also large numbers of passes are granted to soldiers for those days. At any rate the epidemic can not be attributed to conditions within the camp. *Overwork and fatigue* have had no appreciable effect upon the epidemic nor in leading up to it. During the epidemic two hikes were indulged in by the two infantry brigades of the command. On September 20 the 23rd Brigade marched to Cranberry Pond, about five miles from the camp, spent the night in the rain under shelter tents, and returned the following day. On September 28 the 24th Brigade took the same trip. In neither case were any bad results observed by the ever-watchful Division Surgeon. Previous to the hikes the commands were carefully overhauled and every man concerning whom there was the slightest doubt was left behind in quarters. It is this weeding-out that accounts for the rise of the noneffective rate on appropriate days. The *weather conditions* seemed to many to be accountable for a great deal of sickness, for the spread of influenza, and for the frequency of pulmonary complications. An analysis of the data does

not confirm this except in those cases where the men were allowed to take advantage of the execrable weather to remain indoors. The organizations which spent most of the time in the open, and which were therefore most exposed to the weather, suffered least during the epidemic (note the Remount Depot). Fresh air is one factor in this, but separation of individuals is accessory. *Housing*, if one includes in the term overcrowding, has surely been an important factor in spreading the epidemic. Whether it has had any appreciable effect upon the incidence of complications is a question. The epidemic has certainly gone faster and was over sooner because of the crowding; the hospital was filled sooner than it should have been as a result of the rapidity of spread of the disease, and overcrowding of the hospital occurred when with a less rapid spread it would not have occurred; but whether the number of fatalities or the number of pneumonias was greater than they should have been with less crowded conditions may be doubted. Camp Devens was constructed for a maximum population of 35,000 men. At the time of the epidemic there were 45,000 men in it. But the conditions are not told merely by the numbers. Five thousand of the overpopulation were in tents, and this reduced the overcrowding to 5,000. If the weather conditions had not been so miserable just prior to the outbreak of influenza, most of the additional 5,000 would have been in

TABLE VII

EFFECT OF LENGTH OF SERVICE

A. Length of service in men who died of influenza-pneumonia:

Less than 1 month	38
1 month	130
2 months	241
3 months	72
4 months	46
5 months	21
6 months	12
7 months	5
8 months	3
9 months	0
10 months	3
11 months	2
12 months	14
More than 12 months	4
Not given	30
Total	621

B. Data from the Infantry Organizations:

36th Infantry	Strength 3781		
Less than 5 months'	service 975	Influenza	264
More " " "	" 2806	"	302
42nd Infantry	Strength 3757		
Less than 5 months'	service 2182	"	611
More " " "	" 1575	"	124
73rd Infantry	Strength 4241		
Less than 5 months'	service 3593	"	1257
More " " "	" 648	"	210
74th Infantry	Strength 3723		
Less than 5 months'	service 2809	"	1443
More " " "	" 914	"	397

tents. Before the arrangements could be made the epidemic opened. The large number of *recruits* in the camp certainly was a factor in increasing the disease incidence, as shown in Table VII.

Associated with the problem of the recruit is that of *individual susceptibility*. This element is to be evaluated with the greatest circumspection. There are no definite facts to indicate that there are or are not individuals who are not susceptible to the infection. Not until the laboratory has some more definite information concerning the cause will we be able to discuss this question with any degree of satisfaction. For the present it seems that multiplied opportunities for infection play a more prominent role than susceptibility. The *general sanitary conditions* of the camp were excellent before and during the epidemic. The buildings were kept sufficiently warm and at the same time decent ventilation was enforced. It was the rule to require that at least 50 per cent of the upper sashes in each squad room should be kept open during the night. Beds and bedding were taken out of doors and aired on every available day. Tents were kept open as a rule, and were furled on every sunny day. Clothing was ample and there was a sufficient amount of bedding for each man. There was but little dust in the camp, partly because of the general situation of the camp, but largely because of the amount of rain. The barracks were wet-swept and mopped with mixtures of soap suds and oil. There were no mosquitoes and but few flies. The quality and quantity of food was all that could be desired. Promptly after the onset of the epidemic all bunks were separated by shelter tent halves. The men slept with heads and feet alternating.

The problem of the effects of previous life in *cities or in rural districts* was studied superficially as shown in Table VIII.

Very early in the epidemic bacteriologic studies were started. At first these were centered upon the blood and were unproductive—all cultures made from the blood during life remained sterile. Attention was then focused upon the sputum, which, while it had been studied from the start with reference to pneumococcic types, had not been systematically examined for other germs. It was immediately plain that beside the pneumococci and hemolytic streptococci, the sputum contained a small delicate bacillus which was apparently identical with that of Pfeiffer. The coexistence of these various organisms made it a difficult task to isolate the last. From the consolidated lungs three organisms were isolated at autopsies—the pneumococcus, the bacillus of Pfeiffer (?), and a larger bacillus as yet unidentified. From the blood of the heart pneumococcus alone was isolated. Early in the epidemic the routine work claimed every available worker. Later, however, additional and expert assistance was furnished. It is interesting to consider that the streptococci though present in so many mouths seemed to play no part in the pathologic changes found at autopsy. A different state of affairs may develop at other camps.

Special reports on the bacteriology and pathology of the epidemic will undoubtedly soon issue from the laboratory of the Base Hospital. The notes made here are very incomplete. In the postmortem reports filed in the office of the Camp Surgeon the anatomic diagnosis "lobar pneumonia" appears in about two-thirds of the cases. In the remaining third lobular, broncho, or con-

fluent pneumonia are given as the cause of death. It is believed that the essential lesion is a focal one—lobular—which in the course of events may, and does in a considerable number of cases, become more or less lobar in its distribution. The appearances suggest that the pulmonary disease begins as a very severe, and often hemorrhagic, inflammatory edema primarily lobular in distribution, and definitely related to the bronchi. The lungs are intensely congested and even quite generally hemorrhagic but with focal areas of consolidation in the

TABLE VIII

DATA ON URBAN AND RURAL PNEUMONIA DEATHS IN CAMP DEVENS

A. The following data bear upon the distribution of influenza-pneumonia in urban and rural populations. The population figures are not exact and were derived from several sources. They are, however, believed to be sufficiently accurate to serve the purpose for which they were used. All the deaths occurred at Camp Devens.

STATE	POPULATION	DEATHS	RATE PER 100,000
New Hampshire	442,500	43	9.7
Urban	188,900	15	7.9
Rural	253,600	28	11.1
Maine	792,400	115	14.5
Urban	183,900	18	9.7
Rural	608,500	97	15.9
Vermont	363,000	47	12.9
Urban	48,600	5	10.3
Rural	314,400	42	13.3
Massachusetts	3,729,000	215	5.7
Urban	2,585,500	141	5.4
Rural	1,133,500	74	6.5
Connecticut	1,244,500	66	5.3
Urban	597,000	30	5.0
Rural	647,500	36	5.5
Me., N. H., Vt., Mass., Conn.	6,571,400	486	7.3
Urban	3,603,900	209	5.8
Rural	2,967,500	277	9.4

B. The following data bear upon the distribution of influenza-pneumonia in urban and rural populations in Massachusetts. There are not sufficient data available to make a similar comparison in the other New England states.

CITIES	TOTAL POPULATION	DEATHS	RATE PER 100,000
Over 100,000	1,700,000	75	4.4
50,000-100,000	220,000	10	4.5
40,000- 50,000	236,000	12	5.1
30,000- 40,000	143,480	12	8.3
20,000- 30,000	94,500	9	9.5
10,000- 20,000	191,480	23	12.0
Total	2,585,460	141	5.4

TOWNS	POPULATION	DEATHS	RATE PER 100,000
5,000-10,000	128,000	23	17.9
2,000- 5,000	11,500	5	42.6
Total	139,500	28	20.0
Other Towns and Villages	1,004,040	46	4.5

C. It is only in the group of deaths for "other towns and villages" that any discrepancy exists in the series, and this discrepancy can not be explained unless it is possible that the places belong in one of the two former groups. They may be suburbs, for instance, of larger towns and cities.

region of the hilus. They have many of the characteristics of the lungs of animals suffering from hemorrhagic septicemia. From the hila the inflammatory changes appear to extend peripherally following the bronchi. Such true consolidation as occurs is patchy and the areas do not have the gray, dryish, granular appearance of the usual lobar pneumonia. Upon the pleuræ there may be scanty collections of fibrin, and in the pleural cavities there are apt to be accumulations of clear serous fluid. Pericarditis does not seem to be common. The main bronchi, and often the larynx and pharynx are quite congested and even hemorrhagic, a condition which may account for the presence of bright blood in the sputum in many cases. The cervical and peribronchial lymph glands are congested and, at least in some instances, studded with foci of necrosis so that they resemble lesions found in plague.

While it is true that the Medical Department bore the brunt of the fight against the epidemic, it is also true that without the help of the line, officers and men, the battle would have been lost. The line cooperated to the fullest possible extent and helped in every possible way. Nevertheless the strain upon the Medical Department was almost unbearable. At first there were not enough doctors and nurses. Later this lack was corrected.

During the epidemic the regimental infirmaries were kept running day and night, and were subject to inspection at any time in the twenty-four hours. Scarcely a night passed that some one from the Camp Surgeon's office did not drop in at the various infirmaries to see that the work was going on, and to go out with the Surgeon to the barracks to see if any one in need of attention was being overlooked and to see that the squad rooms were in proper order and were well ventilated. On these trips any man who even looked as though he might be sick was examined and if he showed any definite signs he was sent to the hospital or placed in an isolation room for observation. In order to provide for such a continuous medical service for the more than 40,000 men the members of special boards were detailed to the infirmaries or to the Base Hospital. It came about in this way that every medical man in the camp was on constant active duty at the height of the epidemic. The Camp Surgeon was indefatigable in his efforts to see that everything was done that could be done, and deserves the most unstinted praise.

Methods of isolating the bunks in barracks in attempting to control the epidemic have already been mentioned, as have other sanitary methods. Preventive measures other than separating beds, keeping the men out of doors as much as possible, and separating them at mess, do not seem to have been valuable—at least they have shown no decided effects. Just what the study of the whole situation will show the value of masks to have been, remains to be seen. At Camp Devens they were not used. We felt that masking might well be useful provided the masks were properly made and if they were worn with military precision. During such a period of stress as that which prevailed during the epidemic this could not be accomplished. In the Base Hospital previous to this epidemic the surgeons and nurses and attendants have worn no masks and have escaped pneumonia and other diseases very consistently. During the epidemic they did wear them and they have suffered severely from the disease. Visitors at the hospital were required to wear masks. At no time

were the entertainment buildings closed to men, but all gatherings were interdicted and no entertainments were given. Visiting within the camp was permitted only to friends of men on the dangerously sick list.

In conclusion only this can be said, that the epidemic hit Camp Devens at a time when it was unexpected. The attack was unheralded from any source and there were no precedents to guide in its management. From the start more emphasis was placed upon early recognition and hospitalization, and every case was looked upon and treated as a potential pneumonia. Little emphasis was placed upon quarantine and preventive measures except those which kept men out of doors as much as possible and those which kept men apart in barracks and mess halls.

Table IX contains a statistical summary of the epidemic by weeks.

TABLE IX

	SEPT. 4-10	SEPT. 11-17	SEPT. 18-24	SEPT. 25-OCT. 1	OCT. 2-8	OCT. 9-15	OCT. 16-22	OCT. 23-29	SEPT. 4 OCT. 29
Average strength of command	45096	44565	45380	45347	45153	44450	43383	41145	44315
Average white strength	42005	41478	42307	42037	41836	41113	40013	38625	41192
Average black strength	3091	3087	3073	3310	3317	3317	3270	2520	3123
Total influenza cases			*12924	1076	289	135	92	67	14583
Total pneumonia cases	49	102	1020	1415	119	49	30	33	2817
Annual rate per 1000 (pneumonia)	76	157.5	1548	2182	136.9	77.2	34.9	42.3	413
Total pneumonia deaths	3	8	212	437	94	24	5	4	**787
Annual mortality rate per 1000—pneumonia	3.4	9.3	242.2	500	108.2	28.1	6.1	5.9	114
Total black pneumonias	25	30	126	62	25	6	6	18	298
Annual rate per 1000—black pneumonia	421	504	2127	978	393	94.4	95.4	372	619
Black pneumonia deaths	3	0	29	37	12	4	0	2	***87
Annual rate per 1000 black pneumonia mortality	50.4	0	490	581	188	62.6	0	41.2	183
Total white pneumonias	24	72	894	1353	94	43	24	15	2519
Annual rate per 1000	29.7	90.2	1075	1673	116	54	31	20	53.5
Total white pneumonia deaths	0	8	183	400	82	20	5	2	700
Annual rate per 1000	0	10.2	224	494	101	25	6.4	2.7	14.9

*Includes cases reported since Sept. 4.
** = 27.9% case mortality.
*** = 29.5% case mortality.

APPENDIX

Since the preparation of the above notes, a superficial study has been made, which was perforce largely retrospective, of the part played in transmission of disease by methods of washing dishes in the various messes. It may be said, that generally speaking, the common method of washing mess kits is for each man to wash his own kit, and this he does by passing in line before a series of large cans filled with hot water, into which he dips his utensils. The first two of the series of cans are filled with hot, soapy water; the last, with clear, hot water. An alternative method consists in pooling the mess kits and having them washed in the kitchen by the kitchen police. The latter method pre-supposes a better supply of hot water, so that after the final rinsing the kits are drained and dried, and dish towels are done away with. Where this alternative method has been used, the influenza rate has been said to be lower than when the common method is in use (see Lynch and Cumming: *The Military Surgeon,* Dec., 1918, xliii, 597). Special investigation of this aspect of the question indicates that at the Remount Depot, the Quartermaster Corps messes, and in the messes of the 36th Infantry, greater care was exercised in the washing of mess kits, and that at the Remount Depot and Quartermaster Corps, the mess kits were, almost without exception, pooled.

It seems from the indications to date that the matter of hand-to-food, and hand-to-dish transmission is one that may well be considered by health authorities (note its importance at public eating places) and by individuals in their houses.

THE NATURE OF THE LYMPHOCYTOSIS OF ACUTE INFECTIONS

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ONE of the most striking phenomena of the acute infectious diseases is the variation in the absolute number and the relative proportion of the different forms of the white blood cells as observed in the peripheral blood.

Such a study of the leucocyte count is now recognized as one of the most constant criteria for the differentiation of many of the acute febrile infections.

The most striking feature in such conditions, with perhaps the exceptions of lues, pertusses, and typhoid, is an absolute increase in the leucocytes and a relative increase in the polynuclear neutrophils.

Within the past few years a few cases of acute infective lymphocytosis, the nature of which is not at all well understood, have found their way into the literature.

Among these may be mentioned particularly the contributions of F. Marchand[1], and R. C. Cabot[2], the latter reporting five cases, in one of which the lymphocyte count reached as high as 86 per cent.

A critical study of some of the reported cases leaves one somewhat uncertain as to their true nature, and, indeed, it is not always possible to determine whether a given case should be classified as an acute lymphocytosis or an acute lymphatic leucemia as is so well brought out in some of the cases reported by Barker, Baetjer, and Miller[3].

The present paper reports a fatal case of Ludwig's Angina in which a remarkable, so-called, lymphocytosis was observed, and it is my purpose to use it as a basis for a possible criticism of the infective lymphocytoses.

CASE HISTORY

This concerned a young farmer twenty-six years of age, of good family and personal history, and who had just recently been accepted for life insurance, and whose illness began with symptoms resembling a cold in the early part of December, 1915.

About the last of the mouth he visited friends in Oklahoma and returned to his home in southern Iowa in January not feeling quite well and within a few weeks developed a sore mouth, with swelling and redness of the gums and marked salivation.

Notwithstanding the usual treatment for stomatitis the mouth failed to improve and by the middle of February he began to show a slight fever with swelling of the right submaxillary region.

After about two weeks this was opened by a deep incision, and a very little pus and blood secured which showed a diplococcus, thought to be the pneumococcus, and from which a vaccine was made.

He was treated with this vaccine for several weeks during which time the submaxillary swelling subsided and the stomatitis slightly improved.

About the first week of April a swelling rapidly developed under the left jaw and he was referred to me at the Iowa Methodist Hospital on the evening of April 10.

He was fat, but very pale, and had a swelling of woody hardness in the left floor of the mouth and under the left jaw, extending well onto the neck.

The mucous membranes were very pale and the gums so badly swollen as to almost conceal the free margins of the teeth and from which could be wiped away a thrush like exudate and a small amount of pus expressed from their dental margins.

The breath was remarkedly free from fetor, and there was considerable salivation.

The chest was negative except a soft systolic murmur over the cardiac apex, and the spleen was just palpable.

Neither sugar nor albumin was found in the urine.

Blood counts made on the twelfth, during which time the temperature ranged from 101° to 104.8° F., showed hemoglobin 65 per cent erythrocytes, 2,0000,000, slight anisocytosis, an occasional nucleated and a few stippled red cells.

The leucocyte count was 11,000, of which 96 per cent were classed as lymphocytes, mostly of the larger variety.

Almost daily examinations throughout the following week, at which time he died, showed essentially the same condition of the leucocytes, though the total count rose to 15,000 and on the day of death to 23,000.

Cultures from a very small amount of pus secured by radical operation of the submaxillary triangle on April 13 revealed pure cultures of *staphylococcus aureus*.

Blood cultures were not made.

During the last two days of illness swelling occurred in the deep cervical lymphatics of the right side, while the swelling of the left jaw extended to the soft palate, the left eye and the left upper chest.

There was severe, sudden pain in the left eye ball, and hemorrhages occurred from the nose, mouth, and bowels.

Within a few hours after death the body became markedly emphysematous, and at autopsy the internal organs showed the characteristic frothy appearance of *gas bacillus* infection.

Smears and sections from these organs showed this organism present in great numbers.

Without discussing the primary, or the secondary nature of the mouth infection, or the equally interesting relationship of the gas bacillus to the anemia[4], it is interesting to observe that the relative lymphocytosis here observed is greater than that hitherto reported.

Cabot reports 86 per cent in one of his cases, while this case showed 96 per cent.

Unfortunately the fresh slides were only studied with the Wright stain, while those which were preserved at the time were studied months later with Wright's, Giemsa's, and hematoxylin and eosin.

It is greatly to be regretted that these slides were not studied for the leucoprotease and peroxidase reactions, for without these the nature of those cells which we have taken for lymphocytes must remain somewhat questionable, notwithstanding that by the methods employed there was scarcely a question of their nature.

The almost constant and uniform nature of the dominant cell with a simple nucleus and a well developed ring of nongranular cytoplasm left little room for doubt that they were what we have all hitherto regarded as large lymphocytes.

About nine per cent of the total leucocytes are without question the small lymphocytes, and about an equal percentage no one would doubt as large lymphocytes, but these latter grade away insensibly into larger nongranular mononuclear cells which from their morphology and tinctorial properties every one who studied them looked upon as lymphocytes, but which after a more careful study, taken in connection with certain other hematological and clinical features of this case I am inclined to believe are susceptible of another interpretation.[5, 6, 7]

A study of 555 cells from various slides made at various times throughout the last week of illness showed only 13 with distinct neutrophilic granules, while the remaining 542 were classified as nongranular, the total numbers and percentages being as follows:

Nongranular Cells.	Total.....97%.		
	Small nongranular lymphocytes,	51.....	9%.
	Large nongranular lymphocytes,	51.....	9%.
	Large nongranular mononuclears, (lymphocytes?)	424.....	77%.
	Transitional, (indented nongranulars)	6.....	1%.
	Polymorphonuclears, (nongranulars)	7.....	1%.
Neutrophile Granulars.	Total..... 3%.		
	Large slightly granular mononuclears (lymphocytes?)	8.....	1%.
	Polymorphonuclear granular (leucocytes)	5.....	1%.
	Eosinophiles and Basophiles	0.....	0%.

From the above table it is seen that about 95 per cent of the cells are mononuclear, nongranular leucocytes, apparently identical though in some instances slightly larger than the so-called large lymphocyte, and from the blood picture one would hardly hesitate to make the diagnosis of lymphocytosis or possibly lymphatic leucemia, though for the latter the total leucocyte count is very low.

It seemed impossible to conceive that lymphocytes could migrate into the cellular tissues of the floor of the mouth and neck in sufficient numbers to account for the extensive board-like swelling.

We therefore believe[8] that they are the immature histological antecedents of the granular myelocyte; viz., the nongranular myeloblast, and that future studies by the more recent methods will show the leucocyte of the infective lymphocytoses, and most likely the acute lymphoid leucemias to be of myeloid instead of lymphoid origin.

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SOME NOTES CONCERNING HEMOLYTIC STREPTOCOCCUS INFECTION*

By Moyer S. Fleisher, Captain, M.R.C., and C. D. Hamilton, First Lieutenant, M. R. C.

DURING the latter part of March and early part of April, 1918, there occurred at Camp Wadsworth an epidemic of measles and practically concomitant with it an epidemic form of bronchopneumonia associated with empyema.† During this time there were some 200 cases of measles, and 21 cases of bronchopneumonia or empyema in which a hemolytic streptococcus was the causative agent.

In the main the characteristics of this epidemic were similar to those noted in other camps. The number of cases occurring here, however, was not very large, and the infection with the hemolytic streptococcus was confined very largely to the men of two organizations (1st Pioneer Infantry, and 2nd Pioneer Infantry).

Of the 21 cases of bronchopneumonia and empyema, 8 were among men in the 1st Pioneer Infantry, 7 were in the 2nd Pioneer Infantry. The men affected were chiefly men who had recently arrived at this camp and were individuals from sparsely settled districts who were in their organizations brought into contact with men who had been in camp for some time and who came originally from larger cities. It is also interesting to note that two regiments were quartered alongside each other. The other 6 cases were distributed among other organizations. It also seems that in the cases occurring in this camp there was less of a tendency towards the development of metastatic lesions than had been observed at some other camps.

At the same time that this small epidemic existed, a number of other cases of pneumonia occurred, largely, however, of infection due to a Type 4 pneumococcus. As the infections with the hemolytic streptococcus subsided, there was noted a marked increase in the number of pneumonias due to a nonhemolytic streptococcus. This is best seen in the table showing the cases typed for pneumococcus during the months of April and May.

Table 1

	APRIL		MAY	
	SPUTUM	PLEURAL FLUID	SPUTUM	PLEURAL FLUID
Type I	5	1	2	1
Type II	4	0	0	0
Type III	6	2	0	0
Type IV	34	6	2	0
Hemolytic Streptococcus	13	11	2	0
Nonhemolytic Streptococcus	3	4	22	9
Negative	0	6	0	8

The interesting facts presented by this table are, first, that the infections

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†There were also at this time a considerable number of infections of the upper respiratory tract being admitted to the Base Hospital which were probably due to hemolytic streptococcus infections.

with hemolytic streptococci disappeared almost entirely in the month of May, but that in the place of the hemolytic streptococcus there appeared a nonhemolytic streptococcus which was the most important causative agent in the pneumonias occurring during the month of May. Infections with the nonhemolytic streptococcus began to appear in the latter part of April, and concomitantly the infections with hemolytic streptococci fell off in frequency.

It is not our intention to dwell upon any of the aspects of the epidemic of bronchopneumonia and empyema, as it presented, at least from the bacteriologic point of view, but little difference from the conditions noted at other camps. Suffice it to say that in nearly all cases in which hemolytic streptococci were found in the sputum, the same organisms were also found in the pleural exudate. At autopsy, conditions very similar to that described by McCallum as being found at Fort Sam Houston during the epidemic there were seen. Blood cultures during life were negative and the only blood culture which was positive for hemolytic streptococci was taken within twenty-four hours of death, and after the individual had had a resection of a rib done. Culture from the lungs and from the heart's blood after death showed hemolytic streptococci in all cases which were so cultured.

The one aspect of this rather short-lived epidemic upon which we wish to dwell is the occurrence of hemolytic streptococci among the troops of this camp during and after the epidemic. During the latter part of the epidemic and for some time afterwards, we made a survey for hemolytic streptococci of the patients entering the Base Hospital and the patients in the wards of the hospital, which, while not quite as extensive or as exhaustive as we should have liked, does furnish us some rather interesting data.

A first suggestive sign was noted some time before the epidemic appeared. During the latter part of March and early part of April a large number of throat cultures were taken for the detection of meningococcus carriers, these being taken in the 1st Pioneer Infantry, when it was observed that a very large number of these plates showed small colonies about which there was distinct hemolysis. While no examination was made of these colonies to determine whether they were hemolytic streptococci it seems that probably they were and that we had here the primary focus from which the organisms which were later the cause of the epidemic were spread. It should be borne in mind that it was particularly in this regiment that the measles and a large percentage of the hemolytic streptococcus pulmonary infections arose. It was in the regiment quartered in the adjoining quarters that the next largest number of hemolytic streptococcus infections arose.

When the nature of the epidemic was actually noted, a survey was begun of cases admitted to the hospital, of selected suspicious cases and of certain wards in the hospital to detect the presence of hemolytic streptococci in the throats of the patients. As the epidemic was rather short-lived and disappeared rather shortly after its nature was appreciated, our results are not very extensive or as full as we should have liked them to be; nevertheless, we believe that they point in the direction of certain interesting facts.

During the month of April throat cultures were taken from 203 individuals and were examined for hemolytic streptococci, of which 86 were posi-

tive—42 per cent. During the month of May, when the infections with hemolytic streptococci had practically disappeared, a total of 230 were examined and of these only 22 showed hemolytic streptococci—9.5 per cent. These 22 positive cases were noted in the cultures taken in the early part of May and during the latter part of the month only one positive culture for hemolytic streptococci was obtained. The figures just mentioned represent figures for cases admitted, especially selected cases and various wards in the hospitals.

Cultures were taken from cases admitted to the hospital from April 23 on; both medical and surgical admissions were examined: this was done so that we would have cases of a general type and not only medical cases which might possibly represent chiefly cases of tonsillitis, or pharyngitis.

TABLE II

CULTURES AND ADMISSIONS FOR HEMOLYTIC STREPTOCOCCI

	APRIL 2-30		MAY 1-31	
MEDICAL CASES	Total	30	Total	6
	Positive	7	Positive	0
SURGICAL CASES	Total	23	Total	40
	Positive	12	Positive	0
ALL CASES	Total	53	Total	46
	Positive	19	Positive	0

The very marked difference between the cultures taken in April and those taken in May is evident, and it appears that a disappearance of hemolytic streptococci took place about the end of April.

During the latter part of April and early part of May throat cultures were taken from a number of medical cases in which it was suspected that hemolytic streptococci might be present. This was done as a precautionary measure for purposes of isolation of such cases and in order to treat such cases to rid them of the organisms. Between April 23 and April 30, 20 individuals were cultured and 7 were positive. After April 30, 20 more were cultured and only 3 were positive. These figures correspond to a certain extent with the figures noted in the cultures of admitted cases; it should be mentioned that the cultures of selected cases were taken only during the early part of May while the cultures from admissions were taken at various periods throughout the month.

WARD INFECTIONS

In the article by Cole and McCallum it is suggested that the hemolytic streptococci are spread to individuals by transmission while the patients are in the wards. This statement is based upon repeated cultures taken of individuals in measles wards, and it is shown that the longer the individuals are in the wards, the greater the number of individuals showing hemolytic streptococci.

We have not carried out similar examinations, but have in some cases taken cultures from the individuals in certain wards previous to admissions of carriers of hemolytic streptococci to that ward, and have again cultured the

individuals in the ward some time after the admission of the carriers. We have also made several examinations of certain wards. Our results do not seem to point to the fact that ward infection does take place under the conditions existing in general medical wards or in pneumonia wards. We can not, however, give any evidence concerning the possibility of ward infections in measles wards as our investigations do not admit of any conclusions regarding these wards.

On April 22 a positive carrier of hemolytic streptococci was admitted to one of the general medical wards; three days later all the patients in this ward were cultured and only this one individual was found to be positive. It is of course possible that the time elapsing between the introduction of this positive carrier into the ward and the culturing of the entire ward was too short for infection to take place; however, within three days Cole and McCallum noted a marked increase in the percentage of individuals positive for hemolytic streptococci in the measles ward which they examined.

On April 25 the patients in another ward were all cultured and 3 out of 29 were positive for hemolytic streptococci. On April 29 another individual with hemolytic streptococci was admitted to this ward; four days after this last-named individual was admitted, the entire ward was again cultured and only one individual was found to be positive for hemolytic streptococci.

On April 25 a patient in the lobar pneumonia ward was found to have hemolytic streptococci in his throat. The entire ward was cultured three days later and out of 30 individuals only this one man was positive; two more positive carriers were brought to this ward on April 29 and four days later the entire ward was cultured and these original three were the only ones who had hemolytic streptococci in their throats.

Somewhat similar results were noted in still another ward. In no case was there any evidence whatsoever that the introduction of individuals who were carriers of hemolytic streptococci into a ward had any effect in spreading the infection with this organism to the other individuals in the ward; and so-called "ward infection" does not seem to have taken place.

THE RELATION BETWEEN MEASLES AND HEMOLYTIC STREPTOCOCCI

The presence of hemolytic streptococci in the throats of individuals affected with measles has come to be pretty widely accepted. At the time that the measles epidemic first appeared in Camp Wadsworth, the men affected came very largely from one organization (1st Pioneer Infantry) although the other individuals affected with measles were pretty widely scattered so far as concerns organizations. Cultures were made, the last days of April, of the throats of all individuals in two measles wards, and of the 35 individuals cultured 23 showed hemolytic streptococci. In these wards somewhat more than 50 per cent of the individuals came from the 1st Pioneer Infantry. Mumps was also epidemic at this time, and was especially prevalent in the same organization; we took cultures in the mumps ward at about the same time that we cultured the measles ward, and here out of 35 men 18 were positive for hemolytic streptococci. There would appear from the figures above to be some relation between measles and hemolytic streptococci, but certainly not a specific

relation, since the percentage of positive carriers among the individuals affected with mumps was quite as high as among the patients with measles.

During the latter part of May a number of cultures were taken of the patients at that time in the measles wards, and of 61 individuals cultured, none showed hemolytic streptococci. These men were chiefly if not entirely individuals from different organizations from those which had been affected with measles in the previous month and had but recently come to the camp. There seems here to be definite evidence that there is no connection between measles and hemolytic streptococci; and that the previous findings of the prevalence of hemolytic streptococci among measles cases was only chance.

DISCUSSION

It appears from facts gathered during and after a mild epidemic of bronchopneumonia associated with empyema in which the streptococcus hemolyticus was the principal organism, that at the time of this epidemic and probably preceding the appearance of the epidemic there was a large number of carriers of hemolytic streptococci present in the camp. A majority of the cases of bronchopneumonia and empyema occurred in the organization in which it is probable that numerous carriers were present. However, even in patients in the hospital in whom hemolytic streptococci were found in the throat we did not see the development of the streptococcus empyema syndrome; so that it is evident that factors other than the presence of hemolytic streptococci are of importance in the development of this condition. What this may be we can not state. Fox and Hamburger dwell at length in their articles upon the several factors which might be of importance in development of the disease. It is unfortunate that we do not know whether these men who were so severely affected by this condition became infected here or were already affected before they arrived at camp; it is, however, probable that they were carriers before they arrived at Camp Wadsworth. They came to this camp about the middle or the latter part of March and within a few days after their arrival here the organization was cultured for meningococcus carriers, at which time as previously stated they showed apparently a large number of positive hemolytic streptococcus carriers. It is of course possible that they may have been infected before their arrival at Camp Wadsworth, but the fact remains that the streptococci if they were present at the end of March did not become virulent until some two weeks later. Possibly they were gradually acquiring increasing virulence as Fox and Hamburger have suggested.

It has been shown above that ward infection with hemolytic streptococci did not take place here during the height of infection with hemolytic streptococcus. It is possible that under different conditions and dealing with a more virulent infection or possibly with men under different conditions such infections in wards may occur, but it can not be accepted that it does occur as a general thing.

It has also been shown that hemolytic streptococci are not constantly to be found in the throats of individuals suffering with measles, and it would appear that the occurrence of the measles and the streptococcus infections at the same time was simply chance.

LABORATORY METHODS

THE SPINAL FLUID IN EPILEPSY: A PRELIMINARY REPORT*

By John H. Larkin, M.D., and Leon H. Cornwall, M.D.,
New York City

THE bloods and spinal fluids of 146 cases of epilepsy were submitted to routine examinations, consisting of the Wassermann reaction upon each and on the spinal fluids pressure estimations, cell counts, globulin and colloidal gold reactions.

In the bloods the Wassermann reaction was positive twelve times (9 per cent). *Post hoc propter hoc* an etiologic relationship between syphilis and the epilepsy might be presumed to exist in those cases. No such conclusion, however, will be ventured until the associated clinical analyses have been completed, but the incomplete clinical investigation, which includes a search for the evidences of stigmata of congenital lues, indicates to us that there is a causal relation between the two diseases in a much higher percentage of cases.

Diffuse neurosyphilis was present twice and general paresis once. The Wassermann was positive in the spinal fluid in one case of neurosyphilis and in the case of paresis, but in none of the other fluids.

Pressure estimations were made fifty-nine times, of which nine were diminished (15 per cent), 18 were increased (31 per cent), and 32 were normal (54 per cent). The blood Wassermann was positive in one of the nine cases with diminished fluid pressures, and in two of the 18 cases with increased fluid pressure.

Among 143 fluids on which cell counts were made, a pleocytosis was present but once, in a fluid from one of the cases of diffuse neurosyphilis. Six cells were present in two and four cells in five fluids. Twenty-six fluids were acellular and the remainder contained from one to three cells per cm.

The globulin content was tested in 137 fluids. There was a definite increase in 7 (5 per cent) and a slight excess in 22 (14 per cent) with the Ross-Jones modification of the Nonne Phase I reaction. Two of the fluids with a slight excess of globulin came from positive blood Wassermann cases, but none of the fluids with definite globulin increase came from cases with positive blood Wassermanns.

Of all the spinal fluid reactions only the Lange colloidal gold test showed any considerable deviation from the normal. This test was applied 114 times. Fifty-three (46 per cent) were within normal limits. Fifty-two (46 per cent) gave low curves to 2. Eight (7 per cent) gave moderately high curves to 3. The one paretic fluid gave the usual Type 1 or paretic curve. All but two of the fluids from positive serum Wassermann cases gave reactions within the

*From the Pathologic Laboratories of the New York City Hospital.

normal limits. In the two exceptions the curves only went to the shades of decolorization represented by the number 2.

With our present crude methods of studying the chemistry of the spinal fluid there appear to be certain similarities in the effect produced by this secretion on solutions of colloidal gold in epilepsy, nephritis and vascular lesions of the neurospinal axis; in diffuse neurosyphilis and anterior poliomyelitis, and in paresis, multiple sclerosis, lateral sclerosis, brain tumor and eclampsia.

Is epilepsy due to some chemical change in the blood increasing its toxicity and thereby inducing the characteristic explosive motor phenomena after the threshold of tolerance is exceeded? Or are the objective phenomena induced by an increased toxicity of the spinal fluid caused by an altered physiology of the cells of the chorioid plexus, meninges or neural parenchyma?

These questions remain to be answered. Chemical studies of the blood and spinal fluid in epilepsy offer a fruitful field for further investigation.

Colloidal chemistry may furnish a key to the explanation of some of these questions.

METHOD FOR OBTAINING MOUSE BLOOD*

By Holland N. Stevenson, M.D., New York City

THE usual method of obtaining mouse blood for tissue culture has been to take it from the carotid artery. In such a small animal this is a rather difficult technical procedure, and introduces not only a large time factor but also a strong possibility of contaminating the blood with tissue juices. These difficulties have greatly reduced the possibility of *in vitro* work with mouse tissues on any very large scale.

In searching for a method of obtaining mouse blood which would obviate these difficulties, it was found that the intracardiac method of obtaining blood which has been applied to larger animals could be applied to mice with a large measure of success. The object of this paper is to present this application of the method as it has been developed at the laboratory of the Crocker Fund, where it has proved its value during an extensive study of the growth of mouse tissue in homologous plasma.

Syringe.—The type of syringe employed was the 2 c.c. Luer, graduated in 0.1 c.c. The needles were number 22, 1¼ inches long. It was necessary to have a needle with a sharp point, in order that the operation be successful. Two of these needles were wrapped in cloth with the syringe and sterilized by steam. A number of these packages were always kept in the ice box ready for use.

Animal.—The hair was removed from the anterior portion of the thorax. The mouse was etherized and tied out on the animal board. Great care was taken that the forelegs were rather tightly stretched and arranged at an angle of about 60° with the longitudinal axis of the body. The skin was then thoroughly washed with 95 per cent alcohol.

*From Columbia University, George Crocker Special Research Fund, F. C. Wood, Director.

The syringe and needle were thoroughly rinsed with ice-cold olive oil to prevent clotting. The point of inserting the needle varied slightly with the size and position of the animal; usually it was in the third or fourth right intercostal space at a point somewhere between the right border of the sternum and the mammary line. The direction in which the needle was pointed was often determined by the visible pulsation of the heart. This usually became quite apparent when the needle was pressed gently upon the thorax producing a slight depression. Often after the needle had been inserted and had come in contact with the heart, one could feel its pulsations provided the syringe was not held too tightly.

After the needle had been inserted to a distance which should bring it into the heart, a moderate suction was created in the syringe. In a large percentage of instances the blood immediately flowed into the syringe. If this did not occur, the suction was maintained and the needle very slowly advanced and if blood was then not obtained, the needle was very slowly withdrawn. If the blood still did not flow, the needle was withdrawn practically to the surface and its direction changed until the desired result was obtained.

After the blood began to flow, it was essential to hold the syringe absolutely still, for the slightest movement dislodged the point and the operation was unsuccessful.

The amount of blood obtained from one mouse was from 0.5 to 1.25 c.c. The usual amount was 0.75 c.c. The mice did not always die from the operation and many were bled twice, some even three times. The blood obtained in this way yielded plasma which would often remain without clotting for two and one-half hours.

MODIFICATION OF GRAM'S STAIN FOR POSITIVE BACTERIA*

By Joseph Leidy (Philadelphia), Captain, M. C., U. S. A.

In the course of some experiments in staining bacteria according to Gram's method it was found that any of the metallic iodides soluble in water may be substituted for the potassium iodide in Gram's Iodine solution. With the iodides of magnesium, soda, arsenic, aluminum, zinc, iron, both ferrous and ferric, an equally satisfactory result was obtained as with potassium. The iodine dissolves more slowly with ferric iodide and arsenious iodide than with the others, which, however, is not objectionable.

In the case of the ferrous iodide and arsenic iodide, we thought the stain was rendered a deeper hue. This after many trials. As with most microscopic technic, care should be exercised to follow all details.

At the present time, when the cost of the potassium salts is to be considered, the cheapness of some of the others, such as arsenic and ferrous iodide, is worthy of consideration when large quantities may be necessary for laboratory use in class demonstration. The modification is not without value.

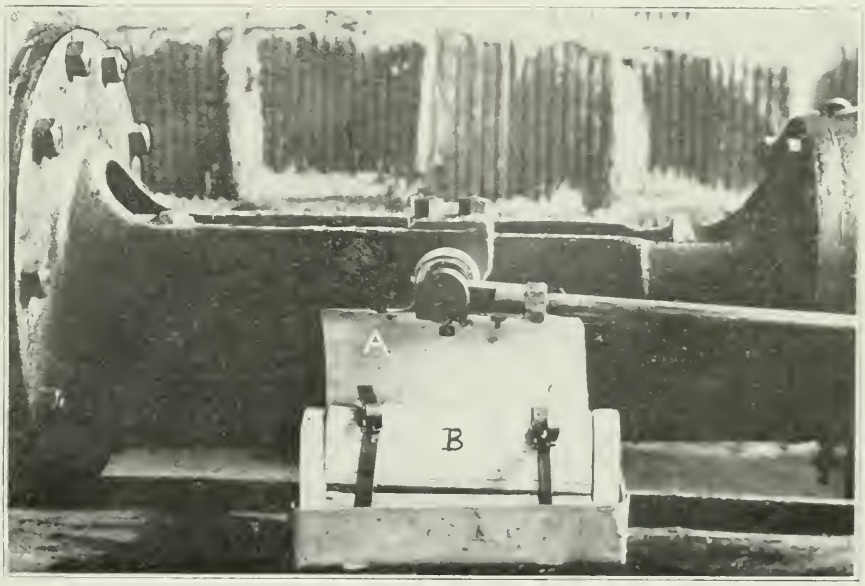
*From the Chemical Warfare Service, Brady Laboratory, New Haven, Conn. Authority to publish granted by the Surgeon General's Office.

A SIMPLE SHAKING APPARATUS

By A. L. Garbat, M.D. (New York City)
Captain, M.C., U. S. Army; Chief of Laboratory, General Hospital No. 12, Biltmore, N. C.

THE only essential is a pump, the piston of which works in a to and fro movement. At our institution, the vacuum pump for the radiator system was found suitable. As is seen in the photograph, the apparatus consists of two parts, (A) a cradle made of metallic sheet iron which is tightly fastened to the side arm of the piston, and (B) the container which consists of a cylindrical block of wood hollowed out in the center and split in half, into which the bottle for shaking is placed.

The containers provided by the Army Medical School for the shipment of bacteriologic material also serve this purpose well. The container is strapped tightly to the cradle. The to and fro action of the piston provides an efficient motion for shaking.



DRAWING FOR AUTOPSY TABLE CONSTRUCTED BY ENLISTED MEN FROM "LEFT OVER" LUMBER*

Reported by Major Fred W. Baeslack, M.C., U. S. A.†

I HAVE thought that it might be worth while to make available for the medical profession the accompanying drawing for an autopsy table constructed by members of the enlisted personnel from "left-over" lumber.

*Published by permission of the Surgeon General.
†From U. S. Debarkation Hospital No. 2, Staten Island, N. Y.

The 12″x12″ sink, the drain connection and metal sheeting, costing from twelve to fifteen dollars, constitutes the entire cash outlay for its construction.

The water is supplied, both cold and hot, from connections above the table, through six feet of rubber garden hose.

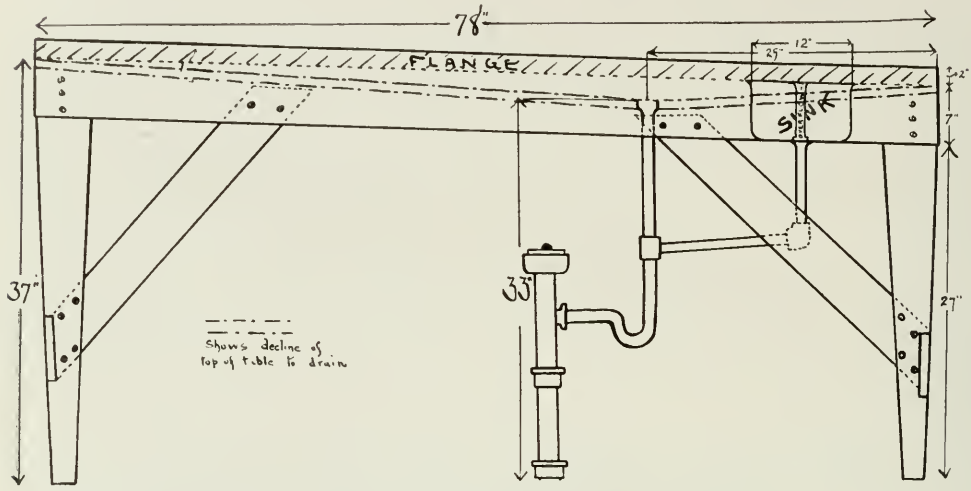


Fig. 1.

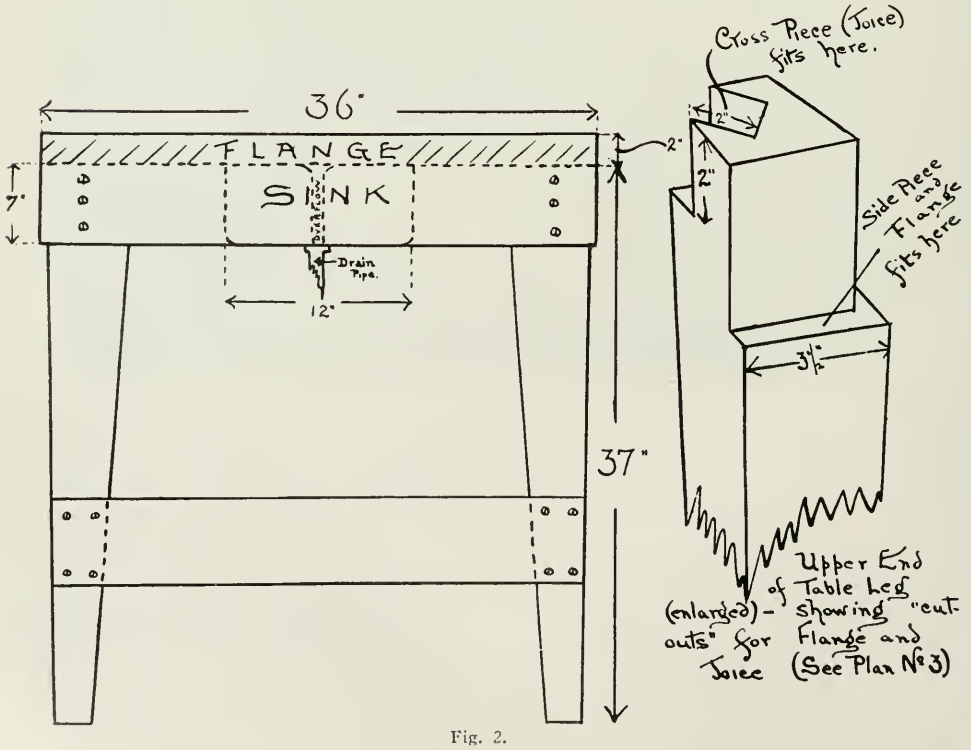


Fig. 2.

The advantages of this table are:

(a) The sanitary construction.

(b) The sink near the foot of the table permits the washing of organs removed at autopsy, and obviates working with soiled hands and instruments.

The accompanying drawings will need no further explanation.

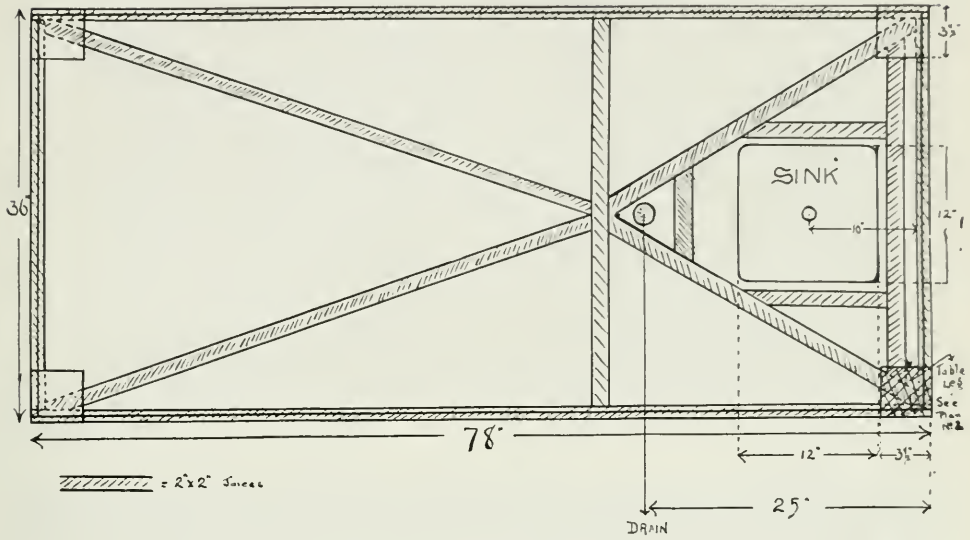


Fig. 3.

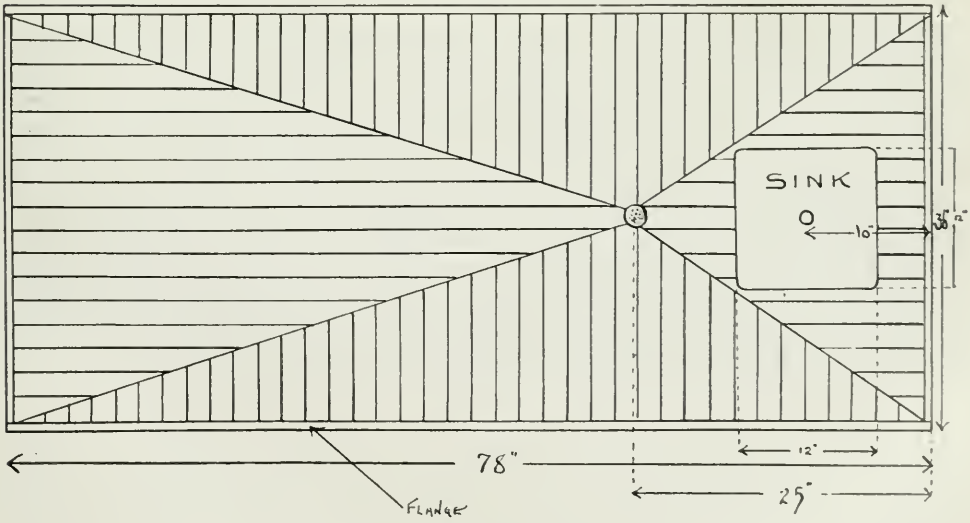


Fig. 4.

A SIMPLE AUTOMATIC KEY FOR USE IN THE STUDENT PHYSIOLOGIC LABORATORY*

By S. Morgulis, Ph.D., Omaha, Neb.

IT is often desirable in experiments performed by students in the physiologic laboratory to employ a key that would permit to make or break the electrical circuit automatically and at exactly the same point. By superimposing a series of curves the effect of various factors is best illustrated since the details of the different curves are thus readily compared. In this laboratory we have used an arrangement which for extreme simplicity and cheapness is most suitable for student work. Furthermore, it has the advantage that each student can make this himself. We used this method for the past three years with considerable success, and in publishing this suggestion we are prompted by a feeling that others may perhaps also find it useful.

The key consists merely of a piece of stout copper wire (No. 18) wound about the screw of a Harvard kymograph by which the sleeve of the drum bears on the steel shaft. It is fastened in position by the set screw. A metal rod (also made by the Harvard Apparatus Company) is clamped in the stand bearing the signal magnet as well as the muscle holder and lever. The rod should be directly above the kymograph and should extend an inch or two beyond the circumference of the drum. As the drum moves, the circuit is closed and opened each time the copper wire glides over the rod. A series of muscular contractions may be recorded in succession, the contractions all rising from the same point on the surface of the kymograph.

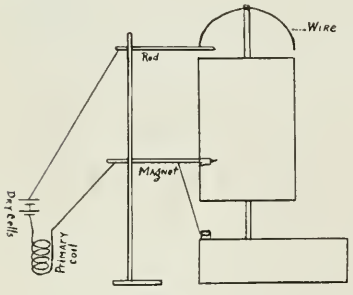


Fig. 1.

The copper wire can be made with two arms, and in this way a double record will be secured for each revolution of the drum; but three or four similar records can be prepared just as easily. As our students work in groups of two, a piece of wire bent in the shape of a semicircle—twisted in the middle to form an eye—is fastened under the set screw, and all records are thus made in duplicate.

The method is so simple that our students with a short experience in the physiologic laboratory get excellent results. I am reproducing records recently obtained by the students, one showing the effect of temperature, the other of fatigue, on muscular contraction (see Figs. 2 and 3).

Of course, the wire must be so adjusted that, as it goes round with the drum, its free ends just barely touch the rod. This is very easily accomplished, securing perfect contact without undue friction which would otherwise interfere with the free movement of the kymograph. Although this key both makes and breaks the circuit, in practice these follow each other with such

*From the Department of Biochemistry and Physiology, Medical College, Creighton University, Omaha, Neb.

rapidity that only a single response of the muscle results. To complete the primary circuit, one lead from the batteries is attached to the rod, while the other lead is fastened to the milled head on the kymograph base which regulated the fast speed. A signal magnet is generally included in the primary

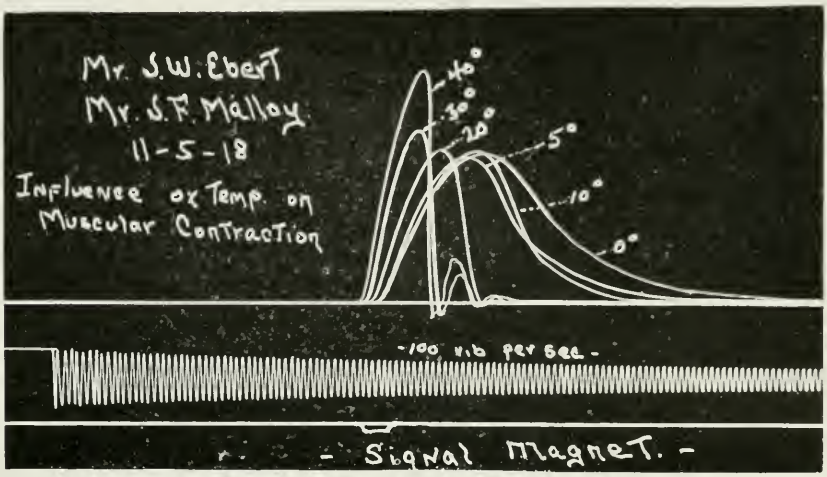


Fig. 2.

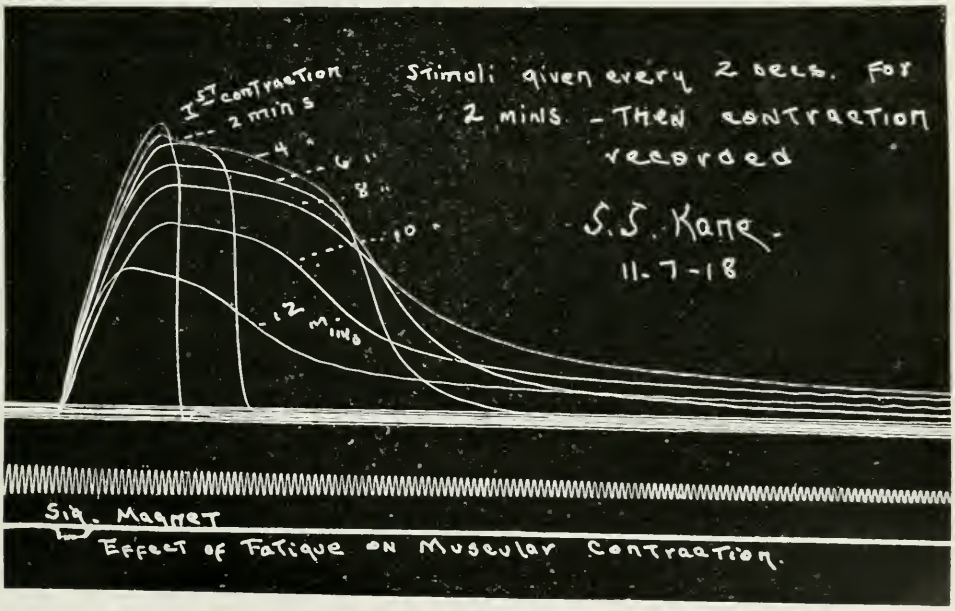


Fig. 3.

circuit. While this method is susceptible of further improvement, the high degree of satisfactoriness of the results does not seem to justify the introduction of other modifications in view of the expense which would be involved.

A TYPE OF SIMPLE KEY FOR LABORATORY USE*

By John A. Higgins, Chicago, Ill.

An important factor in the physiologic and pharmacologic laboratories is the use of some type of a simple electric key. There are a great number of simple keys already on the market, but the majority of these keys seem to receive more or less criticism regarding their laboratory value. The spring type of a simple key, a type which is best illustrated by Jackson,† is quite often criticized where a continuous electric stimulus is desired. The inability of such type of keys to remain closed during continuous stimulus, without constant pressure on the spring in order to make contact, seems to be the main drawback. When interrupted stimulus is desired, the knife switch type of simple electric keys quite often meets with disapproval because of their inability to break contact in as simple a way as can be had with a spring type of key.

Where these various types of simple electric keys have met with disfavor,

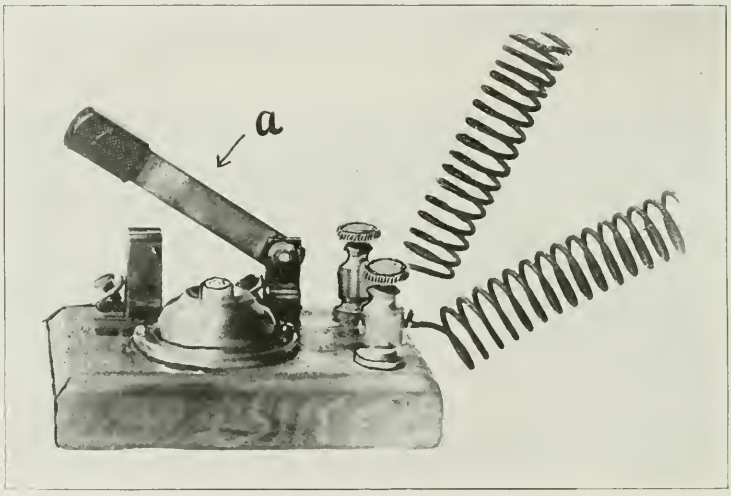


Fig. 1.

it is not uncommon to see the laboratory worker resort to the more expensive telegraph type of key. The telegraph type of key is generally so constructed that for continuous stimulus the key can be closed, without further attention, for any definite period of time, whereas for interrupted stimulus the key can be so adjusted as to give interruptions as often as desired by simple pressure on a knob and for each interrupted stimulus.

The cost of the telegraph key, however, retards its greater use and especially so in the student laboratories. I have therefore devised a key which is inexpensive, yet effective, and can be used to advantage among students as well as research workers. It (Fig. 1) is constructed by mounting on some suitable

*From the Department of Physiology, University of Illinois School of Medicine, Chicago, Ill.
†Jackson, D. E.: Experimental Pharmacology, C. V. Mosby Co., p. 145.

base, and connecting in parallel, a single knife switch key together with an electric door bell push button, two binding posts being used as terminals.

While the material used in the construction of this key has cost me approximately thirty-one cents, which is within the cost of the average laboratory simple key, yet I have a key which is just as effective in the laboratory as the more expensive type of telegraph key. A continuous stimulus while in circuit with an inductorium and electric cell, can be had by closing the single knife switch lever at *A*. The interrupted stimulus can also be received, with the use of the same key, by opening the single knife switch lever and making interruptions with the aid of the door bell push button.

A TYPE OF STIMULATING ELECTRODE*

By John A. Higgins, Chicago, Ill.

A LARGE assortment of stimulating electrodes for use among the medical students, as well as for use among the laboratory research workers, are illustrated as a rule in the different physiologic text books and laboratory manuals. Sanderson,[1] Stirling,[2] Porter,[3] Howell,[4] Jackson,[5] etc., illustrate one or more of this large assortment of available types of electrodes.

A great majority of the stimulating electrodes generally terminate with projecting platinum points soldered to insulated copper wire. While the platinum has a higher resistance than copper towards electric energy still the platinum points are here added owing to its resistance against corrosion, therefore insuring a more perfect stimulus. Jackson,[5] however, has substituted German silver in place of the platinum points without any noted disadvantage.

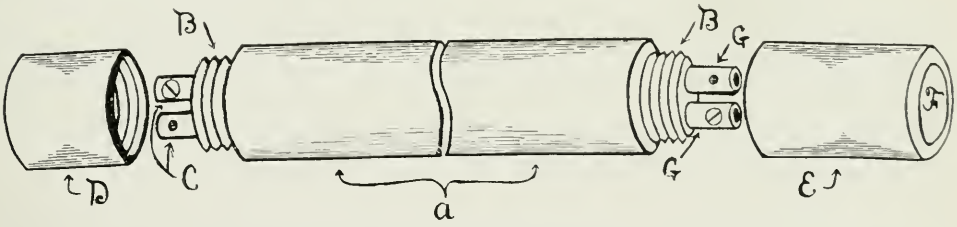


Fig. 1.

While students or other laboratory workers may have success in the handling of electrodes, still it is not uncommon to see platinum points broken off at the soldered connection. When the platinum points break off it necessitates more or less skill and time in resoldering the points into place for future service.

Endeavoring to overcome any disadvantages, as may occur in the older types of stimulating electrodes, I have accordingly designed a new type (Fig. 1). The advantages offered in this new type are first the elimination of platinum points, substituting other inexpensive metals and yet insuring a good electric

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contact on a nerve or other body tissue; second, the advantage of bringing into laboratory services discarded steel phonograph needles, which, no doubt, are plentiful and can be of service until corrosion sets in; lastly, such changes as are deemed advisable can be easily and quickly made by a student or research worker before or during an experiment and without the skill of resoldering connections.

The stimulating electrode as illustrated is constructed from a piece of round, hard rubber rod (*A*) ⅜ inch thick by 3 inches long. On each end at *B* was cut away approximately 1/16 of an inch and threads numbering 32 to the inch were then cut upon the remaining ends. Two holes, using a 3/32 inch drill, were drilled from end to end in the hard rubber rod, allowing approximately 3/64 of an inch between each drilled hole. Two pieces of 3/32 by 3¾-inch brass tubing (*C*) were inserted into the drilled holes of the rubber rod. On each end of these brass tubes holes were drilled and threaded to accommodate 2/56 or smaller size screws. Caps were then made for each end of the rubber rod. The cap on the end which was designed to hold the projecting stimulating points (*D*) need only be long enough to act as a shield for the screw connections (*C*). Both ends of this cap should be fully opened. The cap towards the end of the rod, and to which are fastened the wires from the inductorium, is somewhat longer (*E*), but at one end the opening is only large enough to permit the positive and negative insulated wires to pass through snugly. These caps were made of hard rubber but it might be much easier to substitute metal caps, care being taken to avoid the metal caps coming into contact with the screw heads, etc., on the ends of the brass tubes.

In connecting up the electrode, pass the wires from the inductorium through cap *E* at point *F* and fasten to the ends of the brass tubes at *G*. Screw the cap onto the end of the rubber rod after making contact connections. On the ends of the brass tubes at *C* fasten in uncorroded steel phonograph needles or some similar inexpensive metal and cover up the contact connections with cap (*D*). The electrode is now ready for stimulations. If corrosion sets in on the projecting points from day to day, it will be found an easy procedure to remove cap *D*, replace the projecting points, and rescrew cap *D* into place. Hard rubber material for such electrodes can be supplied by the American Hard Rubber Co., 337 West Madison Street, Chicago, Ill.

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[5]Jackson, D. E.: Experimental Pharmacology, C. V. Mosby Co., p. 65.

MODIFICATIONS OF HENDERSON'S METHOD OF ESTIMATION OF THE HYDROGEN-ION CONCENTRATION OF URINE*

By Howard D. Haskins, M.D., Portland, Oregon

HENDERSON'S[1] method has made it feasible for any careful worker to estimate the true acidity of the urine. This method has been indispensable to the successful accomplishment of several important researches.

There is, however, a difficulty which has undoubtedly deterred many from using the method, namely, that the standards for comparison must be freshly prepared each day that estimations are made. After having had this problem in mind for several years, I have succeeded in preparing artificial standards that retain their proper color value for many months, and that are easily made up anew.

With the modifications proposed in this paper the method can easily be used by any clinician, and furthermore, with very little expenditure of time.

The excretion of strongly acid urine persistently day after day and at all times of day is undoubtedly often of clinical significance. It may furnish a clue to the existence of acidosis or a cardiorenal difficulty, or of some other condition well worth investigation. We are strongly of the opinion that not nearly enough use has been made clinically of the method. The estimation might well be made part of the regular urine examination when a case first comes under observation. Furthermore, it is indispensable in connection with the *alkali retention*[2] test for acidosis. In carrying out this valuable test litmus paper should not be depended on to determine when the urine has become alkaline. The bicarbonate should be administered at regular intervals until the urine comes to a definite H-ion concentration (e.g., P_H 7.4), following the example of Palmer and Van Slyke.[3]

MODIFICATIONS OF HENDERSON'S METHOD

1. *Indicators.*—We have realized for a long time that it is desirable to use only indicators that give a good gradation of red colors. Therefore the use of paranitrophenol was discontinued. Sodium alizarin sulphonate, recommended by Palmer and Henderson[4] did not seem at all satisfactory for our purpose. Rosolic acid was adopted for the range of acidities formerly determined with paranitrophenol.

By using methyl red, neutral red and rosolic acid as indicators, gradations from red to yellow throughout the entire series of the P_H standards are secured. One who is not at all expert can easily detect the difference in color of neighboring standards at every point in the series. With these colors it is easy to make the estimation by artificial light preferably using the new daylight lamp (Peerless Mazda C2).

2. *Acidity Standards.*—For some years we have preferred to use Sörensen's phosphate mixtures for all of the standards (and in the proportions recommended by Sörensen) instead of the mixtures suggested by Henderson. They are much more convenient, and probably more reliable.

*From the Department of Biochemistry, Medical School, University of Oregon.

3. *Use of Bottles.*—In carrying out Henderson's method we soon found that making colorimetric comparison of solutions in flasks was unsatisfactory, so that we adopted the use of French square bottles, the wide-mouth two-ounce colorless bottle being our final choice.

4. *Quantities Used.*—We have reduced the amount of distilled water used in an estimation to 20 c.c. and the amount of urine to 1 c.c. or less. Exactly 1 c.c. of indicator is taken in every case. The water is measured quickly with a graduate.

5. *Distilled Water.*—For research accuracy we found it necessary to use boiled distilled water. For rapid cooling of the water large heavy-walled pyrex test tubes are used. The water is poured into the tube boiling hot, a rubber stopper is inserted and while pressing this down the air is allowed to escape by prying one side of the stopper with a knife blade. The tube can be put into the coldest tap water at once, and the cooling takes but a few minutes. For ordinary routine work unboiled water can be used, but it should be put into a pyrex or nonsol flask when freshly distilled, and the flask must be kept sealed with a rubber stopper *constantly* except when water is being poured out. Distilled water kept in a bottle dissolves alkali from the glass.

Do not allow expired air to get into the flask. Excess of carbon dioxide in the water can change the estimation noticeably in the case of urines that are alkaline or very slightly acid.

6. *Permanent Standards.*—The artificial standards prepared by us to imitate the colors given by the Sörensen phosphate mixtures after the addition of the indicators, are made by adding amaranth and paranitrophenol in various proportions to a buffer mixture which contains KH_2PO_4 and K_2HPO_4, each being in one-tenth molar concentration.

The buffer solution (P_H 6.8) prevents the trace of alkali which gradually dissolves out of the glass of the bottles from changing the color of the standards. This solution gives a decided yellow collor when paranitrophenol is added, the intensity of the color depending on the amount of paranitrophenol used. Amaranth imparts a brilliant red color, and is not affected by the phosphate.

The amaranth and paranitrophenol solutions should be kept in pyrex or nonsol flasks. They do not fade when exposed to diffused light of moderate intensity.

The permanent standards do not change appreciably if properly cared for. They should never be left standing in direct sunlight, and should be kept in a box or cupboard when not in use. Even after nine months our standards were in very good condition, the color changes being so slight as to cause practically no error in estimation of the P_H of a urine.

Each standard is prepared to match somewhat closely the color given by 1 c.c. of a Sörensen's phosphate mixture diluted with 20 c.c. of boiled distilled water after the addition of 1 c.c. of indicator, when at ordinary room temperature (15° to 22°). Absolute matching of the colors is not at all necessary. The use of rosolic acid with urine is possible only with the aid of the permanent standards. Sörensen phosphate standards with rosolic acid change color too rapidly for practical use.

For these permanent standards 20 c.c. of the buffer phosphate solution is put into each of the two-ounce square bottles and various amounts of amaranth and paranitrophenol are added as indicated below, and a little preservative (0.2 c.c. 10 per cent thymol in chloroform) is added, then the bottle is corked (but not with a rubber stopper), and sealed with hot paraffin.

PERMANENT STANDARDS AND THE CORRESPONDING SÖRENSEN STANDARDS

PERMANENT STANDARDS			SÖRENSEN STANDARDS		
			PROPORTIONS IN 10 C.C. OF MIXTURE		
P_H	AMARANTH C.C.	PARANITRO-PHENOL C.C.	1/15 MOLAR KH_2PO_4 C.C.	1/15 MOLAR Na_2HPO_4 C.C.	INDICATOR
4.5 (4.49)	1.3	0.2	10.0	0.0	Methyl Red
4.95 (4.94)	1.0	0.45	9.9	0.1	Methyl Red
5.3 (5.29)	0.65	0.75	9.75	0.25	Methyl Red
5.6 (5.59)	0.45	1.1	9.5	0.5	Methyl Red
5.9 (5.91)	0.25	1.0	9.0	1.0	Methyl Red
5.9 (5.91)	0.55	1.0	9.0	1.0	Rosolic Acid
6.25 (6.24)	0.7	0.9	8.0	2.0	Rosolic Acid
6.45 (6.47)	0.9	0.85	7.0	3.0	Rosolic Acid
6.65 (6.64)	1.0	0.65	6.0	4.0	Rosolic Acid
6.8 (6.81)	1.15	0.3	5.0	5.0	Rosolic Acid
7.0 (6.98)	1.3	0.4	4.0	6.0	Rosolic Acid
7.0 (6.98)	0.6	0.45	4.0	6.0	Neutral Red
7.15 (7.17)	0.6	0.65	3.0	7.0	Neutral Red
7.4 (7.38)	0.43	0.6	2.0	8.0	Neutral Red
7.5 (7.48)	0.38	0.65	1.65	8.35	Neutral Red

The exact P_H figures for the Sörensen phosphate mixtures are those given in the parentheses. The approximate figures can be used for most work, since it is impossible to detect differences between solutions that vary by less than 0.05 in their P_H figures.

The concentrations of amaranth and indicator solutions* are as follows:

Amaranth (amaranth No. 107, secured from Eimer and Amend) 8 mg. dissolved in 100 c.c. of distilled water to which is added 0.5 c.c. of the thymol-chloroform preservative.

Paranitrophenol, (furnished by Eimer and Amend) 20 mg. dissolved in 10 c.c. of alcohol and diluted with 90 c.c. of distilled water.

Methyl red (Kahlbaum's) very finely powdered, 2.4 mg. dissolved in 100 c.c. of 60 per cent alcohol.

Rosolic acid (Merck's) powdered, 16 mg. dissolved in 100 c.c. of 95 per cent alcohol.

*Hynson, Westcott and Dunning, Baltimore, have agreed to supply a partial or complete equipment for carrying out the method as described in this paper. The indicators and other chemicals will be supplied in weighed portions ready to be dissolved, so that those who do not have access to a fine balance will not be prevented from using the method. The samples of indicators purchased from certain other dealers were found by the author to be worthless or weaker in indicator value than Kahlbaum's, Merck's and Grübler's preparations.

Neutral red (Grübler's "zu Injekt. i. vital. Gew. nach Ehrlich") finely powdered, 3.2 mg. dissolved in 100 c.c. of 50 per cent alcohol.

For these solutions the concentrations of alcohol need not be exact.

All the solutions should be kept in pyrex or nonsol flasks. The last three indicator solutions must be protected from the light, preferably by painting the flasks black. These indicator solutions can still be used satisfactorily when two months old, although the rosolic acid weakens slightly in that time. After nine months all the solutions had changed so that they were inferior to freshly prepared solutions. In that length of time the rosolic acid became so much weaker that it required the use of 1.3 c.c. instead of 1 c.c. The methyl red and neutral red did not fade appreciably, but the character of the colors given by them was somewhat different as compared with the colors given by fresh solutions. New solutions might be prepared once in two or three months.

TECHNIC OF ESTIMATING THE P_H OF URINE

All glassware used, (bottles, pipettes, flasks, etc.) must be thoroughly washed, rinsed with distilled water, and then tested with a practically neutral indicator solution, (e. g., 20 c.c. distilled water, 1 drop of the buffer phosphate solution and 1 c.c. of rosolic acid). If the test solution becomes less red, contaminating acid is present, if it becomes redder, alkali is present; in either case wash the apparatus and test again. Rinse out the traces of indicator solution with distilled water and proceed with the estimation.

First make a preliminary determination as follows: to 20 c.c. of distilled water in a two-ounce square bottle add 1 c.c. of rosolic acid solution, and immediately add the urine 0.2 c.c. at a time comparing with the rosolic acid permanent standards after each addition until either the P_H determination remains constant or the urinary pigment changes the character of the color. Never use more than 1 c.c. of urine. In the case of highly colored concentrated urine 0.2 or 0.4 c.c. will suffice. This test indicates the amount to use in the final test, i. e., less than will give the disturbing pigment effect but still enough to give the full P_H estimation.

The test also shows which indicator must be used. If the mixture is as yellow as the 5.9 rosolic standard or more yellowish, use methyl red. If it is as red as the 7 rosolic standard or of a deeper red color, use neutral red. If the color is intermediate between that of the 5.9 and 7 standards, use rosolic acid.

For the final test add to 20 c.c. of distilled water the amount of urine determinated by the first test, and last of all 1 c.c. of the proper indicator. Compare with the standards *immediately* (because contamination with CO_2 occurs so easily, and in the case of rosolic acid the color fades rapidly). Avoid getting expired air into the bottle.

It is self-evident that one must be careful to compare the urine mixture only with those standards that correspond to the particular indicator used (for instance, after using rosolic acid for the urine do not match up with the colors given by methyl red or neutral red). It is advisable to have each standard bottle labeled with the indicator, e. g., Methyl R. 5.3, Ros. 6.8, Neutral R. 7.4; thus accidental slips will be avoided.

The P_H figure of the permanent standard that most nearly matches in color the urine test solution is reported as the P_H of the urine. One may guess P_H readings intermediate between the standards although such interpolation is an unnecessary refinement.

We have found that the most accurate and most rapid estimations are made by placing the standard bottle and the urine bottle for comparison against a background of dull white paper with the light (diffused daylight or the special electric light referred to above) passing over the shoulder.

Very little time is required for making estimations.

REMARKS AND EXPLANATIONS

1. In the above discussion it has been taken for granted that the reader understands what is meant by the P_H. For fear that some may not recall it, I shall explain briefly. The P_H figures are the (negative) logarithms of the true hydrogen-ion concentration. For example, a neutral solution is a 0.0000001 normal solution of hydrogen ions; the logarithm of this decimal fraction is –7.0, therefore, the P_H is 7.0 (the minus sign is ignored). The smaller the figure the greater the acidity.

Urine is seldom more acid than 4.5, nor more alkaline than 7.5 (except when sodium bicarbonate, citrate or similar drugs are taken).

2. Toluol is to be added to the urine as a preservative when collecting a 24-hour sample or when the urine can not be examined within an hour after being passed. The urine must not be treated in any other way, not even filtered. If it is turbid it may be centrifuged.

3. Urines containing hemoglobin, bile or great excess of pigment may be dialyzed in a collodion sac against neutral 1 per cent NaCl solution for thirty minutes, as in Rowntree's[6] method for P_H of blood. The P_H of the salt solution is then determined in the same manner as urine.

4. The room must be free of fumes of NH_3, HCl or HNO_3 when estimations are made. Excess of CO_2 (from flames) should be avoided.

5. For measuring amaranth and paranitrophenol solutions and also the urine, 1 c.c. pipettes marked in 0.01 c.c. are needed.

6. When the temperature of the room is above 22° an error may be made in estimation due to the temperature (the permanent standards do not change perceptibly), for instance, if the urine test mixture is at 30° the P_H figure will be greater (more alkaline) than at 20° by about 0.05 (in the case of a distinctly acid urine) up to even 0.20 (in the case of an alkaline urine). This can be obviated readily by cooling the distilled water to about 15° before using it.

7. The presence of protein in the urine does not interfere with the use of any of the indicators.

8. The phosphates for preparation of the buffer solution must be pure. I used Baker's C. P. KH_2PO_4 and Merck's pure K_2HPO_4. The buffer solution must have a P_H of 6.8 when estimated by the same dilution method as in the case of urine.

Dissolve each phosphate separately in about 200 c.c. of distilled water taking 6.808 gm. of powdered KH_2PO_4 and 8.712 gm. of powdered K_2HPO_4.

Mix the solutions and dilute to exactly 500 c.c.; saturate with chloroform and filter. Keep the solution in a pyrex or nonsol flask, tightly corked.

9. A slight precipitate may appear after a time in the permanent standards, but this need not interfere with their use if they are not shaken up.

10. Test the indicator solution at least once a month by making P_H estimations with Sörensen's phosphate mixtures (1 c.c. diluted as in estimating urine), using for methyl red the P_H 5.3 mixture and for neutral red the P_H 7.15 mixture. For rosolic acid the buffer phosphate mixture can be used (P_H 6.8). This procedure also assures one that the permanent standards have not changed enough to cause inaccurate P_H estimations.

11. The distilled water may be tested at any time by adding to 20 c.c. two drops of the buffer phosphate solution and 1 c.c. of rosolic acid, the color must be redder than the 6.65 standard but not redder than the 6.8 standard. The distilled water should not be too old.

SUGGESTION OF A NEW WAY OF EXPRESSING ACIDITY OF THE URINE FOR CLINICAL PURPOSES

Many persons do not readily grasp the idea of the P_H notation and quickly forget the explanation. It is also confusing to many that the P_H figure should become smaller as the acidity increases.

In devising a new notation advantage may be taken of the proportion of acid phosphate (KH_2PO_4) in the Sörensen standards. For instance, a phosphate standard having a P_H of 6.8 is a 50:50 mixture of the two phosphate solutions, and contains an equal number of molecules of each phosphate in 1 c.c. of solution. Its acidity may therefore, be called 50 (not 50 per cent). The P_H 4.5 phosphate standard contains only the acid phosphate and would be assigned an acidity of 100. The full notation would be as follows:

PH	CLINICAL ACIDITY FIGURE	PH	CLINICAL ACIDITY FIGURE
4.5	100	6.65	60
4.95	99	6.8	50
5.3	97.5	7.0	40
5.6	95	7.15	30
5.9	90	7.4	20
6.25	80	7.5	16.5
6.45	70		

The use of the expression *per cent* should be avoided because per cent refers to the proportion of substance by weight. Sörensen's alkaline phosphate solution is a 1.187 per cent solution, and the acid phosphate is a 0.907 per cent solution. The percentage of the total phosphate present as KH_2PO_4 in a phosphate solution of acidity 80 (P_H 6.25) is actually 75 per cent. Also the acidity figures do not indicate the relative concentration of hydrogen ions present in solution, for example, a Sörensen phosphate solution of P_H 4.95 contains about 100 times as many H ions per cubic centimeter as a phosphate solution of P_H 7.0, but the relation of the acidity figures is 99:40.

Although it is true that the acidity figure indicates the percentage of the total number of phosphate molecules that are present in a solution as KH_2PO_4 molecules, *it is advisable to refrain from using the term per cent.*

SUMMARY

Modifications of the somewhat difficult standard method are proposed which should enable the physician to estimate with ease and with considerable accuracy the true acidity of the urine. A new notation for the various degrees of acidity is also suggested that may make the method easier for clinicians.

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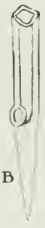
A COMBINED MEASURING AND INJECTING PIPETTE*

By George B. Roth, Washington, D. C.

In order to conform to the U.S.P. method for the physiologic assay of the members of the digitalis series it is necessary to use small amounts of the modified drugs. The transfer of small amounts of fluid from a measuring pipette to a glass container and then to an injecting pipette introduces a slight error which can be avoided by the use of the following described pipette. The combined pipette serves not only for the measuring of the drugs, but for their injection as well. Its use prevents the loss of fluid and shortens the time required for making a series of injections.

The pipette is made from the barrel of an all-glass tuberculin syringe or preferably from a short glass delivery pipette which has a capacity of 1 mil. and which is graduated to 100ths of a mill. (See *A* in illustration.) The lower end of the syringe, or pipette, is drawn out into a fine point similar to an injecting pipette with the exception that the extreme point is closed and pointed sharply. Near the closed pointed end is a small opening. (See *B* in illustration.) The closed point being sharp permits of the easy entrance of the pipette into the anterior lymph sac of the frog while the position of the lower opening of the pipette, being above the extreme point, prevents the opening from being clogged with tissue when the lymph sac is entered. Gravity is sufficient for the injection of the fluid so that the amount introduced can be carefully controlled by admitting air into the upper opening of the pipette.



*From the Hygienic Laboratory, U. S. Public Health Service.

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EDITORIALS

Medical Education in Great Britain

MEDICAL education in Great Britain does not differ widely from that of this country. The minimum requirement is university matriculation which is practically the same as ours of graduation from a first-class high school. The medical course in the British medical schools covers a minimum of five years, but one year of this time is given to chemistry, physics and biology which are included in our premedical course. In fact, one year of credit is given in British medical schools to those who have already passed in these subjects. In the British medical schools Latin is no longer an essential requirement. It will be seen from the above statements that the requirements for admission to the British medical schools are equivalent with us to graduation from a high school with the addition of one year of collegiate work in physics, chemistry and biology. Our Standard Class A medical schools are in advance of the British medical schools so far as admission requirements are concerned.

In the British medical schools the course is divided into the following three groups:

(a) Preliminary Science
(b) Intermediate,
(c) The Final.

The first corresponds to our premedical work, but demands only one year in time. The second is given wholly to anatomy and physiology, and covers two years of work. (It may be remarked that this is an indication of why English medicine has held a predominant rank in anatomy and physiology.) In the third period British medical students have bacteriology, pathology and all the clinical branches and two years of time are given to this period.

Our British colleagues stress examinations much more than we do, and since these are held only at fixed times there is often much delay in the progress of the individual, and six and even seven years may be given to the medical course, and often are, by the average medical student. In some schools students are permitted to take examinations on the completion of each of the three above-named groups. In other schools no examination is held until the completion of all the course. The average cost to the student of his medical course is about five thousand dollars.

The *British Medical Journal* (August 31, 1918) has the following to say concerning the effect of the war on the number of medical students: "Between the years 1910-14 the annual entry of first year medical students averaged roughly 1,440. Since the war the number of these entries has increased by five or six hundred a year. Thus, the whole number of students actually pursuing medical studies in the schools of the United Kingdom has shown an upward steady movement. In May 1916 the total was 6,103; in June 1917 it was 6,682; in October 1917 it was 7,048; while the latest figure for May 1918 was 7,630. But for some time the large withdrawls of male students from medical schools for combatant service, or as surgeon probationers in the navy, more than nullified the increased entries, and bade fair to produce a serious deficiency of new probationers in the years 1918-1919. Urgent representations upon this matter were made to the Government; as a result something has been done to make good the threatened shortage by the return of third year students from active service to complete their studies, by the retention in the medical schools of students on their way to qualifications who are liable to be called to the colors, and by limiting the period of service of surgeon probationers. The Minister of National Service has further undertaken to provide that, if possible, the supply of students in training shall be kept at a level sufficient to give an annual yield of at least 1,000 practitioners."

The number of female medical students has greatly increased and stands now at about 2,250. It seems from the above that the probabilities are when this war closes the number of medical practitioners in Great Britain will be sufficient to supply the demand.

The full effect of the national insurance put into operation before the war on the profession can not be yet determined. It has certainly greatly reduced

the incomes of many of the more expert practitioners, and has increased that of the less efficient. It is impossible to predict the state in which the profession will find itself when the war ends. It is possible, and indeed highly probable, that the socialization of the profession will be greatly advanced. Whether this will be for the good of the profession, or for the good of the people, or for the good of both, will depend upon the lines upon which the advance is made. Great wisdom is needed to direct this procedure.

Most of the universities in Great Britain give courses and degrees in public health. These courses are open only to those who are qualified to practice medicine. They can not be shorter than nine calendar months, and include four months of laboratory work in which chemistry, bacteriology and the pathology of diseases of animals transmissible to man are taught. Six months are given to the questions of health administration and attendance at least twice weekly for three months at a hospital for infectious diseases. While Public Health Service falls far short of perfection, it must be admitted that, judged by the results, it is the best in Europe. There is no other European country in which infections are so well controlled and the death rate so low. This training in public health has been of the greatest service during the present war, both in the civilian and the military population. The service is not uniform, and much is left to local initiative. Appointments are made by local boards. The medical officer of health in a country borough—a designation which includes nearly all the larger towns—is a permanent appointment. The medical officer to a district of 50,000 or more must hold a diploma in public health. School medical inspectors are appointed by the local school boards. The function of the school inspector is broader than it is with us. He must not only watch for infectious diseases, but for physical and mental defects which he must report to the parents and aid them in securing remedies. Not infrequently the office of health supervisor and that of school inspector is held by the same individual. These duties may be shared by an assistant. Under the Insurance Act tuberculosis officers take charge of dispensaries devoted to this disease. These are whole time officials who have special training and the salary is $2,500.

A large proportion of medical practitioners in Great Britain do not possess the degree M.D. In fact, the matter of medical degrees and the number and variety of bodies conferring such degrees is too complicated and too uninteresting to us in this country to justify the time, energy or space necessary to learn it. In our College of Surgeons we are imitating our British confreres. Whether this move is a wise one or not, someone else may discuss.

—*V. C. V.*

Transmission of Influenza

DESPITE the quite tremendous amount of work that has been done in attempting to clarify and elucidate the etiologic problems connected with influenza, very little of practical importance has been evolved. The virus is still

uncertain, if not indeed unknown. Suspicion implicates, depending largely upon the results of bacteriologic work, both B. influenzae (Pfeiffer) and the pneumococci. Also, depending upon the unproductiveness of bacteriologic labors, and of experimental work, certain workers hold to the conception that an unknown filterable virus is the probable essential cause of the complex.

Influenza undoubtedly belongs to the group of diseases which have come to be called "respiratory." It seems surely to be, so far as we can judge, a "spray-borne" disease, by which is meant that the virus is transmitted by spray, resulting from coughing and sneezing, from the respiratory tract of one individual to that of another. There seems to be good evidence also that it may be carried on the hands, and even by dishes, as well as by handkerchiefs and towels. Judging from the rate of spread from person to person the infectious agent is of considerable pathogenicity. Despite all these facts no one seems to have been able to isolate the virus, and only in a few instances has experimental work indicated the definite presence of the virus in the respiratory secretions.

In October 1918, Nicolle and Lebailly concluded from their experiments that the bronchial expectoration of influenza patients is virulent for human beings and for monkeys. These writers used the material from a patient who had been ill two days for inoculations. Filtered and unfiltered specimens were used. The unfiltered substances were inoculated into monkeys by the subjunctival and nasal routes, and in each case caused the disease. The filtered material was used upon human volunteers to whom it was given subcutaneously and intravenously. Those inoculated subcutaneously contracted the disease; those inoculated intravenously did not. Blood taken from a monkey suffering from the disease and introduced subcutaneously in humans did not produce the disease. From these experiments it is concluded that the cause of the disease is a filterable virus which does not inhabit the blood stream, but which does inhabit the respiratory tract.* These early experiments were carried out in an exceedingly small scale.

Following the French investigation, have come the ones carried out under the auspices of the United States Public Health Service and the United States Navy. These have been carried out in two parallel series, one at Boston, Mass., and one at San Francisco. At each, the same methods were used, and consisted in inoculations of human volunteers with pure cultures of Pfeiffer's bacillus, with secretions from the upper air passages, and with blood from typical cases of influenza.†

The studies were begun with an experiment in which a suspension of a freshly isolated culture of Pfeiffer's bacillus was instilled into the nose of each of three nonimmunes and into the nose of each of three immunes. None of the subjects showed any reaction after the treatment. Another experiment was made at a later date with a suspension of a number of pure cultures of the bacillus. Ten nonimmune volunteers were inoculated with negative results. Three sets of experiments were made with secretions,—both filtered and unfiltered,—from the upper respiratory tract of typical cases of influenza in the most active stage of

*Compt. rend. Acad. d. sc., 1918, clxvii, 607.
†Public Health Reports, 1919, xxxiv, 33.

the disease. In these experiments a total of 30 men were subjected to inoculation by means of sprays, swabs, or both, of the nose and throat. The interval elapsing between securing secretions from the donors and inoculation of the volunteers was progressively reduced in these experiments so that in the third of the series the interval at most was 30 seconds. In no instance was an attack of influenza produced in any one of the subjects. An experiment was made in which the members of one of the groups of volunteers which had been subjected to inoculation with secretions were exposed to a group of cases of influenza in the active stage of the disease in a manner intended to stimulate conditions which in nature are supposed to favor the transmission of the disease. Each of this group of ten volunteers came into close association for a few minutes with each of ten selected cases of influenza in the wards of the Chelsea Naval Hospital. At the time the volunteers were exposed to this infection the cases were from ten to eighty-four hours from the onset of their illness and four of them were not twenty-four hours after the onset. Each volunteer conversed a few minutes with each of the selected patients, who were requested to, and coughed into the face of each volunteer in turn, so that each volunteer was exposed in this manner to all ten cases. The total exposure amounted to about three-quarters of an hour for each volunteer. None of these volunteers developed any symptoms of influenza following this experiment.

Advantage was taken of the opportunity for making this study to attempt to confirm the reported positive results of transmission of influenza by Nicolle. Secretions from five typical cases of influenza were secured, filtered, and some of the filtrate was inoculated subcutaneously into each of the group of ten volunteers. At the same time blood was drawn from the same cases and pooled, and some of the mixed blood injected subcutaneously into each of another group of ten volunteers. The time lost between drawing the blood and inoculating it in no case exceeded three-quarters of an hour. None of the men subjected to these inoculations developed any evidences of illness.

The San Francisco observations were made practically simultaneously with those described above. In the parallel series the volunteers who were used differed from those used at Boston in two respects—first, the personnel of the Yerba Buena Station had not been exposed to influenza in the present epidemic and were therefore presumed not to possess any special natural immunity; second, all of the men had been vaccinated with large doses of a bacterial vaccine containing Pfeiffer's bacilli, the three fixed types of pneumococci and hemolytic streptococci. We are not prepared at present to state what influence this vaccination may have had in promoting resistance to influenza infection, but if we may judge by the results of controlled experiments elsewhere such vaccination may for the present purpose be ignored. One group had instilled into the nostrils of each man a heavy suspension made by emulsifying cultures of eight strains of Pfeiffer's bacillus without filtration. The other group had the same material used after passage through a Berkefeld N candle. The results were negative, though the men were held under observation for seven days.

Emulsions of secretions from the upper respiratory passages of active cases of influenza from 15 to 48 hours from the onset were instilled into the nose by

means of a medicine dropper or with an atomizer. In each experiment approximately an equal number of volunteers were treated with the same emulsion after filtration through a Berkefeld N candle. In every case the results were negative, so far as the reproduction of influenza is concerned. The men were all observed for seven days after inoculation.

A filtered emulsion of material from the upper air passages of an acute case of influenza was dropped into the conjunctivæ of two volunteers and the same material injected subcutaneously into one volunteer. In each case the result was negative.

One cubic centimeter of blood taken during the active stage of influenza was inoculated subcutaneously into one volunteer with negative results.

Judging from these three important pieces of experimental work one would say that influenza was transmitted with a very considerable degree of difficulty, and yet the facts observed during the epidemic indicate that the reverse is true. One may reasonably suspect that there are essential conditions, especially in the American series, which inhibited transmission. The positive results of the French investigators overbalance the negative ones of the American. To arrive at certain results further work must be done with subjects who are certainly nonimmune. Before that can be done some method of determining immunity must be devised. —*P. G. W.*

Hand to Mouth Infection

WE have long recognized the fact that the hand of all the members of the body is most frequently the bearer of infection. Long before we knew anything about bacteria it was the custom of decent people to wash their hands before eating. The most ignorant mother sends her little boy from the table when he comes with dirty hands, and tells him that it is not necessary for him to eat the proverbial peck of dirt. The surgeon has spent much time in investigating the methods necessary to so thoroughly cleanse his hands that they may not serve to carry infection to the wounds upon which he operates. He found that sterilization of the hands was difficult and so uncertain that he resorted to the use of rubber gloves. It is true that bacteria may be carried without harm into the mouth which would endanger life if introduced into the wounds; however, that the hand often serves to carry harmful organisms to the mouth and to the respiratory organs is conceded by all.

In army life the soldier is instructed to wash his hands before eating and after visiting the toilet. When one has watched the soldier, the average soldier complying with this order, he recognizes how unsatisfactorily it is done. Possible methods for securing more perfect cleanliness of the hands among soldiers have been the subject of serious and prolonged discussion among medical officers. The same is true concerning the cleaning and sterilization of mess kits. Order after order has been issued concerning this matter, and still, however observant, the medical officer is well aware of the unsatisfactory results obtained.

Recently Col. Lynch and Lieut.-Col. Cumming have called attention to this matter from a somewhat different standpoint than has been done at any previous

time. These officers have shown by statistics that the respiratory diseases are less prevalent among soldiers who use table ware than among those who use mess kits. The usual method of cleaning the individual mess kit is as follows:

A garbage can is filled with hot water, boiling water to start with, in which soap is dissolved. The volume of the contents of the can is subject to considerable variation, but is limited at most to a few gallons. In this two hundred and fifty mess kits are sometimes washed. The water, boiling at first, rapidly lowers in temperature, and soon reaches that of the optimum growth of bacteria. Each soldier puts his hand in the water and scrubs his mess kit. Lieut.-Col. Cumming has made a study of the bacteria in the wash water. In the first place he finds that the number of bacteria removed from the hands depends upon the temperature of the water, that in water from 38° to 50° the number of bacteria removed from the hand and consequently distributed in the wash water is larger than at lower or higher temperatures. He has shown that by the time the Company mess kits have been washed in one of these cans, the fluid has become a rich culture and may contain more than one hundren thousand bacteria per cubic centimeter. Every soldier's hands have been immersed in this fluid. After scrubbing his mess kit in the soapy solution, the soldier dips his mess kit, or is supposed to, in boiling water. This is not always done, but granting that it is done and that that portion of the kit which is immersed in the boiling water is sterilized, what is the condition of the hands which have been immersed in the bacterial culture? This is really more important than the sterilization of the mess kit. The soldier with his hands moist with this fluid rich in bacteria, puts his hands to his mouth, picks his teeth with his fingers, holds the fruit which he eats, hands food to his comrades, opens doors, infecting the knob, spreads the infection over his clothing, and distributes to others the various bacteria present in the wash water. Some of these bacteria he may carry under his nails for days.

The main point brought out by Col. Lynch and Lieut.-Col. Cumming is the infection of the soldier's hands in washing his mess kit. This is of more importance than the failure to sterilize the kit.

There are other ways in which our hands become the bearers of infection. We blow our noses into our handkerchiefs, handle the handkerchief both while it is still moist and after it is dry, then shake hands with our best friends, transferring bacteria along with the greeting.

The story is told of a wicked woman who wore a ring in which there was a spring which moved a fine sharp lancet. When she affectionately and tenderly grasped the hand of her dearest friend she pressed the spring and inoculated her friend with a deadly poison. This is probably all fiction; but how many have been inoculated by the handshake of a friend, no one can tell.

There are various ways in which mess kits can be sterilized. This is a comparatively easy problem; but how to keep the hand free from pathogenic germs at all times is a wholly different and much more difficult proposition.

Workers in bacteriologic laboratories are in the habit of washing their hands in various disinfecting agents. Some use a 10 per cent solution of crude lysol. This is not an unpleasant application, and when allowed to remain upon

the hands for some moments and then washed off with sterile or even safe tap water seems to be efficacious. Probably the most common constituent of the sterilizing jar for washing the hands in the bacteriologic laboratory is a solution of mercuric chloride, one to one thousand. However, this is not efficient. The mercuric chloride coagulates protein substances, and in the coagulent, germs may be entangled and protected from the action of the disinfectant. For this reason the solution of mercuric chloride is not to be recommended. In other laboratories a 5 per cent solution of carbolic acid is used. This is not so agreeable an application as the 10 per cent solution of lysol and probably not so efficient. In still other laboratories the jar for washing the hands contains a saturated aqueous solution of chlorine gas. In my opinion this is the most satisfactory agent for the sterilization of the hands. Of course the chlorine must be washed off the hands with water. Since chlorine is used in almost every camp in the sterilization of water, it might be possible to provide a solution of this kind in which soldiers could wash their hands.

At any rate we must admit that the possibilities of hand to mouth infection are great, and some provision should be made whereby the ill effects may be reduced to a minimum.

—*V. C. V.*

The Toxin of Bacillus Influenzae

THERE are two features of the disease influenza which point to its being due to the action of a powerful toxin, one is the consistent leucopenia,—the other is the rapidity of its onset and extreme prostration. Since there is no certainty regarding the bacterial cause of the disease a search for a toxin must be based upon purely empiric grounds. Since B. influenzæ is under suspicion, and since comparatively little is known of the biologic activities of this organism certain recent studies have centered about it. Most interesting of such studies is that recently published by Julia Parker* on toxin production. Her results are astonishing, and indicate that the organism produces a substance of great toxicity under the conditions of the experiments, i. e., after growth on veal infusion media. "The poison is produced with remarkable speed. We have obtained very toxic filtrates even after only from six to eight hours' incubation. At this time the organisms are growing very rapidly. Most of our work has been done, however, with eighteen or twenty hours' growth. There is no relation between the amount of growth and poison formation. After incubation the cultures were centrifugalized, and the supernatant fluid was filtered through a Berkefeld candle. The sterile filtrate was then inoculated intravenously into rabbits. The poison deteriorates very quickly, even when kept in the ice box. For this reason the toxicity of the poison must be tested, and the experiments made on the same day. If 2 c.c. of a poison killed a medium sized rabbit in from one to three hours, we considered it a good poison. Sometimes rabbits died when injected with 1 c.c. of a poison, but this was not the usual result. When

*Jour. Am. Med. Assn., 1919, lxxii, 476.

a rabbit is given a lethal dose of the poison, there is an incubation period of about thirty minutes before any symptoms appear. This is followed by increasing weakness, often accompanied by diarrhea. Death usually occurs within three hours, with or without convulsions. Immunologic tests were carried out as follows: Rabbits were immunized to multiple lethal doses of the poison. The serum of rabbits that have withstood at least four lethal doses of the poison will protect normal animals against lethal inoculation of the poison. An immunity against a poison produced from any one strain will protect against a poison from any other strain. This protection is shown in two different ways:

"A. By mixing the lethal dose of the poison *in vitro* with the serum before inoculation.

"B. By giving the serum fifteen minutes before or fifteen minutes after the injection of the poison."

These experimental results may be used in explanation of many of the clinical facts of the disease, and also of the discrepancies which appear in the human experimental work in connection with influenza.

—*P. G. W.*

The Human Tubercle Bacillus—Are There Distinct Types?

BROWNLEE,* who has a reputation among his colleagues as "being very learned and more capable of extracting truth from statistics than is any one else in England," has suggested from statistical analysis of the Registrar-General's returns of mortality from phthisis that we may possibly be dealing with three types of the human tubercle bacillus.

As is pointed out in an introduction by the Medical Health Committee of the National Health Insurance to "An Investigation Into the Epidemiology of Phthisis in Great Britain and Ireland," by Dr. John Brownlee, the knowledge of types of pneumococcus, dysentery, typhoid, meningococcus and possibly tetanus, would lead to a suggestion that there might be separate types of the tubercle bacillus causing phthisis. What is novel is "that the detection of distinct types should come sooner from statistical than from bacteriological analysis." Brownlee's studies and charts suggest that we may be dealing with three types of the human tubercle bacillus.

1. The "young adult" type. Death resulting between 20-25 years.
2. The "middle age" type. Death resulting between 45-50 years.
3. The "old age" type. Death resulting between 55-65 years.

These types are shown to have different geographical distribution in Great Britain. Charts are given showing for instance that in the Shetland Islands only the "young adult" type exists, whereas in London practically only the "middle age" type exists.

The statistics of the Registrars-General of England, Scotland and Ireland which are analyzed cover a period of over fifty years, and it is probably rightly claimed that these statistics can be matched by no other country.

*An Investigation into the Epidemiology of Phthisis in Great Britain and Ireland. National Health Insurance, His Majesty's Stationery Office, London.

Inasmuch as populations of certain sections and cities are found to vary in age constitution, a ratio is given between the number of deaths from phthisis and the number of persons living at the same age period, this death rate being expressed in parts per thousand or per million.

The diagrams show that a great diminution in the mortality of phthisis has occurred in the last fifty years, but that this decrease is unequally distributed over the different ages.

A most conspicuous fall in the death rate is noted at the ages twenty to twenty-five, and this in spite of the disease at this age period being the easiest of all to diagnose.

The curves embracing the whole of Great Britain have been generally known. The analysis of returns from limited areas have not heretofore been plotted, and it is a study of these that has led Brownlee to suspect the possibility of the different types.

Data from every county in England were investigated and in this manner the striking age distributions were found. The "young adult" type was generally noted throughout England and Wales with the exception of Lancashire, part of Yorkshire, Staffordshire, Warwickshire and London. In these regions the type of "middle age" phthisis was especially high. It was not possible to analyze Ireland by counties but as a whole it shows a preponderance of the "young adult" type.

Mortality curves contrasting North Wales and London are most striking. They serve to convince one that combined mortality curves of England and Wales would have masked important observations and deductions. In North Wales for the period of 1861 to 1870 the "young adult" type registered nearly 7000 deaths per million living at that age, rapidly declining to 4000 per million in middle age. The 1891 to 1900 period also shows a rapid rise to the "young adult" type, but only registering 2700 per million and the record remaining almost horizontal until sixty-five years. In London, on the other hand, the curve rises to a maximum in both the periods 1861-1870 and 1901-1910 between the ages of forty-five to fifty-five years, 6500 per million for the former and 4500 per million for the latter. The "young adult" type is remarkably slight in amount being 4000 per million in the former and only 1700 per million in the latter.

In general Brownlee notes that the chief seats for the early phthisis are in seaboard and agricultural counties, so much so that in the Shetland Islands there is almost no phthisis at all except this "young adult" type. He suggests, therefore, that Hippocrates may not have been incorrect in his statement that the chief ages of the susceptibility to phthisis were between 15 and 35 years. This would seem to be true today in Wales, a country comparable to Greece.

Cornwall would seem to be a county especially conspicuous for the "old age" type, and it is shown that this has nothing to do with the tin mining industry inasmuch as the incidence is the same in the population not engaged in this work.

It is noted that in Northampton and Leicester, the chief seats of the boot and shoe manufacture, early phthisis is frequent; consequently there is a con-

siderable amount of early phthisis among the boot and shoe makers. It is pointed out that the incidence of pulmonary tuberculosis in different trades must be compared with the incidence and type in the immediate neighborhood and not with that at large.

There is found to be three times as much "old age" phthisis among males as among females, and in females the "young adult" type is a little later than among males, and the "middle age" type a little earlier than among males.

The effect of environment is considered and the following results are suggested: phthisis of the "middle age" type is an infection of which the virulence is increased by the presence of unhealthy conditions, but phthisis of the youth and "old age" types is infection of which the spread is not affected by such conditions.

The idea that an infectious disease is not necessarily more abundant where there is more overcrowding is instanced in regard to scarlet fever. Figures on scarlet fever have been published showing that as room density increases the amount of scarlet fever decreases and that in the best parts of the city of Glasgow there is nearly three times as much scarlet fever as in the worst. When spread by milk, however, notoriously the opposite is found.

It is estimated that a small positive correlation found between the "young adult" and "old age" types indicates that a small number of people can become infected by the tubercle bacillus in youth, hold it at bay during the years of manhood, but succumb to the infection in old age, but most of the cases of "old age" tuberculosis must be regarded as new.

So far only Parts I and II of Brownlee's studies have been published and further publications will be awaited with interest. Should bacteriologic studies confirm his suggestions, practical results may be expected, as he suggests in the more specific tuberculins which may be prepared for each type.

The evidence produced indicates that the epidemiology of the two chief types of phthisis, namely, the "young adult" and "middle age" types, is different. The present epidemic of phthisis of the former type had its maximum about the middle of the last century, while the epidemic of phthisis among the middle aged had its maximum fully one hundred years ago.

The increase in the mean age at death from phthisis which has been steadily rising and which has been explained as due to more immunity and better hygienic conditions of the population would also be possible of explanation by the disappearance of the "young adult" type of disease.

Brownlee's contributions are both stimulating and refreshing and they will certainly give an impetus to laboratory and statistical studies in America.

The great reduction noted in the serious pulmonary tuberculosis at the age of twenty-five would serve to indicate that in our army so largely composed of young men we at present may not expect a large incidence of men returned from France with this disease.

—*G. B. W.*

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ORIGINAL ARTICLES

ENCEPHALITIS LETHARGICA

By Victor C. Vaughan, M.D., Ann Arbor, Mich.

NEWSPAPER reporters are now busy interviewing the doctors concerning the new disease popularly known as "sleeping sickness." In my opinion, any real information on this subject should be given to the newspapers. The time has long since passed when knowledge concerning disease, and especially epidemic disease, should be withheld from the public. The better newspapers in the country now go to the best doctors for information along these lines, rather than, as formerly, to quack nostrum venders. The wise physician uses every legitimate effort to educate the public, and the agency through which this can be best accomplished is the reputable newspaper which constitutes the most important agent for the diffusion of knowledge among the masses. Even the most alert and up-to-date physician knows little about this disease, and the purpose of this writing is to gather together and make available to the profession the more technical details concerning it. I learn from the English review of the foreign medical press that a monograph on encephalitis lethargica has been published at Vienna by Professor Economo. I have not seen this monograph, and herewith introduce the greater part of the notice as it appears in the English review. The statement is as follows:

"In this monograph Economo has republished in readable form the results of his investigations into the epidemic of infective encephalitis, which occurred in Vienna in the winter of 1916-17 without adding much to our knowledge of this interesting disease. Details of thirteen excellently described clinical cases (two of which are new) are given. Of these thirteen cases, five died and were examined both macroscopically and microscopically after autopsy. In all cases the Wasser-

mann reaction in both blood and cerebrospinal fluid was negative (difference from poliomyelitis), and all were tested serologically against various strains of the Bacillus typhosus. The infective encephalitis of man can be conveyed to apes. The cause of the illness, according to the author, can neither be a toxin nor a poison, but must be due to a living organism. This organism can not pass through a Berkefeld filter, and in this respect differs entirely from the organism of poliomyelitis (Heine-Medin disease). From an infected ape a pure culture of a diplostreptococcus was obtained by von Wiesner. This organism when injected into animals produces in those animals a hemorrhagic encephalitis; in some instances in man the encephalitis has also shown hemorrhagic characters. The author discusses adequately the various symptoms; the mode of onset, the fever, the delirium, the somnolence (which he attributes to the localization of the pathologic lesions in the neighborhood of the optic thalamus), the meningismus, the changes in the cerebrospinal fluid, blood, urine, the ocular symptoms, the signs of bulbar interference, the palsies of the extremities, rigidity, athetosis, ataxy. No known measures of therapy have influenced the course of the disease. Excellent descriptions of the changes found in the central nervous system in cases which have died in the active and in more quiescent stages of the infection are given. The descriptions are illustrated by 12 drawings. The author is of opinion that infective encephalitis is pathologically an inflammation of the parenchyma of the central nervous system, complicated by a secondary small-celled infiltration of the vessels.

"A comparison of the lesions found at autopsy, with the findings in cases of dementia paralytica, sleeping sickness, rabies, poliomyelitis, the Borna disease of horses and acute multiple sclerosis, is made and the conclusion reached that infective encephalitis differs from all these. And, finally, it is stated that 'the infective polioencephalitis lethargica is a disease which may assume an epidemic form (as Nona, as the Tübingen sleeping sickness, and perhaps as Morbus Guerlier and as in Vienna) just as can poliomyelitis, but that sporadic cases are always turning up, and that the disease is due to the earlier described diplostreptococcus.'"

We learn from the Lancet of January 11 that the disease has been made reportable in England. A recurrence this spring is predicted. The suggestion that the disease might be due to food infected with the Bacillus botulinus has been investigated by the local government board with a negative conclusion. The same board has reached the decision that this disease is not anterior poliomyelitis, but is a disease *sui generis* of unknown causation. It belongs to the class of polioencephalitic diseases which are inflammatory in nature, but the inquiry has not yielded any conclusive evidence as to the character of the causal agent. When it is considered that the organism which causes the analogous disease, poliomyelitis, is still a matter for debate, although thousands of cases have been investigated from the bacteriologic point of view, it is not surprising that the problem of the causal agent of encephalitis lethargica is as yet unsolved.

McNalty suggests that the relation of this disease to anterior poliomyelitis may be similar to that of paratyphoid to typhoid. He also stresses the influence of lowered resistance, due to war conditions, as a result of which a saprophytic organism may become pathogenic. According to James, this idea is further

strengthened by the widely scattered and sporadic prevalence of the disease. Marinesco and McIntosh emphasize the similarity of the lesions with those of anterior poliomyelitis, especially in the cellular infiltration around the smaller veins in the basal ganglia, the upper part of the pons, particularly in the gray matter of the floor of the fourth ventricle, and to a much less degree in the medulla. Both failed to find evidence of a specific organism, and inoculations of monkeys were without effect.

On May 5, 1918, Netter gave a most interesting paper on this disease before the Paris Academy of Medicine. About two months earlier many cases were seen in the hospitals and in private practice in Paris. The striking symptoms were somnolence, drooping of the upper eyelids, accompanied by mild fever. Though meningitis was the first diagnosis, its characteristic symptoms,—Kernig's sign, rigidity and irregularity of the pulse—were wanting or in doubt. Lumbar puncture yielded normal fluid with no increased pressure. The disease continued for weeks and about 50 per cent of the infected individuals died. Macroscopically there were congestion of the meninges and scattered hemorrhages in both the gray and white matter. Microscopic examination showed cellular infiltration, especially marked about the blood vessels. The lesions were most numerous and most marked in the medulla, pons, and basal nuclei of the brain. Netter regards the disease as an encephalitis of unknown causation, and recalls the fact that under the name "Nona" such a disease was reported in the spring of 1890, especially in Northern Italy and Hungary, but here and there over a large part of Europe. As early as 1712 a similar disease following a pandemic of influenza was reported in Germany and locally known as "Tübingen sleeping sickness." Recently, this disease was first reported at Vienna in the winter of 1916-17. Netter rejects the idea that this disease is anterior poliomyelitis. Lethargic encephalitis, he says, is a disease of winter and spring, while anterior poliomyelitis prevails in summer. The former is much more common in adults, although no age is absolutely exempt. In both, interstitial encephalitis is found, but the involvement of the ganglionic cells, so pronounced in poliomyelitis, is slight in lethargic encephalitis. He also rejects the idea that it is a form of botulism, because if this were the case, it should appear among those who eat at the same mess, whereas multiple cases of the new disease in the same household have not been seen.

Batton and Still (Lancet, London, 1918, i, 636) report an epidemic stupor in children. The report covers four cases, aged three and one-half months, four, seven, and eleven years. The stupor developed rapidly without convulsions, though in one case it was preceded by a listless state. All were brought to the hospital in a state of stupor with the eyes closed, the legs extended, and the arms sometimes flexed, sometimes extended. There was general rigidity of the muscles, but the limbs could be placed in any position and then showed a tendency to remain where placed—a cataleptic state. Although apparently unconscious, they could be aroused and then they slowly responded to inquiries. When asked to open their eyes there was a flickering movement through the muscles before the act was accomplished. When the lids were lifted passively, the eyes were found to be divergent. All swallowed normally, and even when in apparent stupor took readily of the food brought to their lips. The babe nursed when

placed at the mother's breast. At first there was a slight elevation of temperature, but this passed in a few days, while the stupor continued for weeks. The respirations were normal and the pulse regular except in one case which showed some irregularity. The reflexes, both superficial and deep, were normal. The cerebrospinal fluid flowed under normal pressure and revealed no abnormality. The blood showed no abnormal condition, and the Wassermann test was negative. After from three to five weeks the stuporous condition gradually passed away. No two of the children were from the same family, and no other member of any of the families presented similar symptoms. The babe had had no other food than that drawn from its mother's breast, and so far as could be determined, she was in health. An anonymous writer (Lancet, London, 1918, i, 715) commenting on the above report, thinks that the cases have been reported too soon; that the children will not fully recover but will die and autopsy will show either tuberculous or pneumococcal meningitis.

McCaw, Perdran and Stibbing (Lancet, London, 1918, i, 616) report six cases under the diagnosis of toxic bulbar paralysis, and attribute the same to botulism. These cases seem to differ in some details from those reported by others. In two, the spinal fluid flowed with increased pressure. In one, the antemortem temperature reached 109.° There was no evidence of meningitis, and the only detectable lesion was slight edema with some congestion of the floor of the fourth ventricle. The same condition is reported in the three fatal cases. Microscopic studies had not been made at the time of the publication of the report.

Harris (Lancet, London, 1918, i, 568) under the diagnosis of botulism reports six cases. One of these was most probably a case of true botulism. This man ate sausage in the morning and lobster for lunch and spent the night in vomiting. After this he was drowsy, developed bilateral ptosis with divergent strabismus, inability to swallow, and retention of urine. An organism "resembling the Bacillus botulinus" was found in the stools and urine.

The first official report of this disease in England seems to have been made January 26, 1918. Most of the cases so far reported have been in London, but there have been cases scattered all over England and Wales. In only one instance have there been two cases, and one of these was mild and of doubtful diagnosis, in the same family.

Porthier (Jour. Am. Med. Assn., 1919, lxxii, 715) reports eight cases of this disease from Camp Lee in Virginia, with one death. In the fatal case autopsy showed no marked abnormality in the cord. In the brain, the following is a statement of the findings:

"On section of the hemispheres, the centrum ovale presented dilatation of the blood vessels, which appeared as small, punctate bodies throughout the surface. On inspection, the corpus callosum appeared normal; but on attempt to section, it was found to be soft and mushy. All the tissues of the lateral ventricles were soft. The optic thalamus was softened. The velum interpositum and the chorioid plexus presented the same condition as the vessels of the surface of the brain; that is, the vessels were prominent, tortuous and arborescent. There was no excess of fluid in the ventricles, but all the tissues surrounding them were softened, the brain substance as well as the tissues of the floor. The third ventricle presented nothing of note, except general softening of the tis-

sues of the floor. The pineal gland was swollen. The iter a tertio ad quartum was patulous. On section of the basal ganglions a small hemorrhagic spot was found in the right hemisphere immediately adjoining the internal capsule. This spot was about 1 mm. in diameter. On the left side, the basal ganglions presented nothing of note. Anteroposterior sections through the hemispheres presented nothing of note. Sections through the cerebellum presented nothing of note. There was, however, a universal softening of the brain tissue which made it very hard to section without destroying it in the attempt. After sectioning, the organ was apparently collapsed, and there was no possibility of returning the sectioned portion back to the former relation on account of this softening."

The several patients came from widely separated organizations in the camp. The chief symptoms were vertigo, diplopia, headache, slight fever, and the spinal fluid showed a definite pleocytosis (from 20 to 66 cells) of the lymphocytic type.

Wilson (Lancet, London, July 6, 1918) states that the general symptoms are apathy, lethargy, drowsiness, and absence of initiative. In some instances there may be marked restlessness, alternating with profound indifference. Delusions and hallucinations may be manifest. The temperature may be either above or below normal. Paralysis of accommodation with indistinct vision is an early symptom. The drooping of the eyelids may be bilateral or unilateral. The facies is often expressionless with obliteration of the lines on account of a bilateral paralysis. The affection of the cranial nerves is motor, and not sensory. Rarely the limbs are involved, but this is due to disturbance in the cortical paths and not to invasion or involvement of the cord. The spinal fluid is usually normal and pleocytosis is the exception and occurs only when the meninges are involved. This author gives the points of differentiation from poliomyelitis, some of which are as follows:

1. In the latter disease, the lethargic element is wanting.
2. Lethargic encephalitis is most frequent in winter; poliomyelitis in summer.
3. The former is more common in adults; the latter, in children.
4. In encephalitis lethargica the spinal fluid is normal.
5. Meningeal symptoms are more frequent in poliomyelitis.
6. Two or more cases in the same family have not been seen in lethargic encephalitis but is a common observation in poliomyelitis.

In botulism there are no inflammatory lesions in the brain. This is an anatomic condition, and of course can be discerned only at autopsy. Drooping of the eyelids is the most common sign in encephalitis lethargica and is present in at least 75 per cent of the cases.

McNalty distinguishes seven types of the disease. These are as follows:

1. The affection is limited to the third pair of cranial nerves.
2. The brain stem and the bulb are involved.
3. The chief affection is in the long tracts.
4. There is an ataxic type.
5. The cerebral cortex is the chief center of the involvement.
6. There may be signs and evidence of spinal cord involvement.
7. The polyneuritic type.

In England during the spring of 1918, there were 168 officially reported cases, with 37 deaths. The disease seems to have disappeared in June, 1918, but reappeared in the fall of that year.

It must be evident that the time has not come when anything but tentative statements can be made concerning this disease. From the literature, we gather that it is a disease principally involving the brain itself; that there is in many cases more or less involvement of the meninges but this is not prominent. In no case is the cord involved. The stupor is partly apparent and partly real. The real stupor is due to the cerebral involvement. The apparent stupor is due to partial paralysis of the motor nerves employed in lifting the upper eyelids. Coma is not a symptom of the disease.

It is more than probable that a great variety of conditions will be reported as encephalitis lethargica. Already it has come to my knowledge that claims are being made for special treatment in this disease by persons who have never seen it. Only a few days ago, a masseur wrote that she had frequently treated this disease with the best results in the southern states, and that it had followed typhoid fever. There is no authentic case on record in which this disease has followed typhoid. Is it a sequela to influenza? The only reason, and it is a good one, for suspecting that such is the case is that in the past it has followed a pandemic of influenza. To say that one has not had influenza does not mean that influenza is not an essential forerunner of the disease. Most people who have lived through epidemics of influenza, even when there has been no recognizable appearance of the disease in them, have acquired at least a temporary immunity to influenza. The natural conclusion to draw from this is that in a large number —indeed in the majority of people in the midst of an epidemic of influenza— the virus affects the people sufficiently to give a temporary immunity, and it may be that the virus of influenza without causing recognizable acute symptoms may after weeks or months produce the changes in the brain observed in encephalitis lethargica.

EPIDEMIC CEREBROSPINAL MENINGITIS AT CAMP CODY*

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DURING the winter of 1917-18, the occurrence of epidemic cerebrospinal fever in many, if not in all, of the army and navy cantonments was a source of considerable apprehension for all concerned. Long before the discovery of the meningococcus, epidemic meningitis was known to be a serious menace to the armed camp. It was dreaded especially in camps of new, unseasoned recruits.

True to form, meningitis appeared in the European armies promptly after their mobilization in the present war. It became a very serious problem in some of them. Medical officers predicted with certainty that the disease would appear in our own forces, which it did just as soon as any considerable number of recruits were assembled in close quarters. It could not be foretold how extensively or how rapidly the disease would spread within camps, nor was it known whether an epidemic could be thwarted or controlled among such large numbers.

According to a report of communicable diseases in the army by Vaughan and Palmer,[1] Camp Jackson, South Carolina, Camp Beauregard, Louisiana, and Camp Funston, Kansas, suffered most heavily among the army camps, from meningitis (all forms were included in their report.) I was stationed at Camp Funston during the months of November, December, 1917, and January, 1918, and can certify that the epidemic of meningitis there was, next to pneumonia, the most serious medical problem of the camp. On account of quarantine, isolation of carriers, and sanitary measures instituted against the spread of the epidemic, it caused a much greater dislocation of training activities than did pneumonia.

Early in February, 1918, Camp Cody seemed to be threatened with a similar experience. Two cases of meningococcus meningitis had developed in December, 1917, and three in January, 1918. Four cases developed during the first ten days of February. During January some troops were transferred here from Camp Funston where the percentage of carriers had been found to be high. Another factor deserving consideration at that time, was the question of the influence of the sand and dust storms which are prevalent at this camp during the winter and spring. Many cases of chronic, low-grade rhinitis and pharyngitis were attributed to this cause, and that such a condition of the nasopharyngeal mucosæ might favor the growth of meningococci was regarded as a possibility. The combination of these various circumstances was somewhat alarming.

QUARANTINE MEASURES

Realizing the possibility of a serious outbreak, stringent measures were taken to safeguard the command against the spread of the disease. Organization surgeons were directed to be on the alert for symptoms, however mild, of meningitis, attention being called to the extreme importance of early diagnosis and

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treatment. In order to unify the preventive measures, a circular letter was sent to each surgeon, setting forth both general and specific directions to be followed regarding quarantine, reports, and the culturing of organizations for the detection of carriers. The following extract from the letter of instruction indicates the specific procedure to be followed in organizations developing a case of meningitis:

1. Strict quarantine will be maintained until the company or unit is released by a report of cultures for carriers.

2. The contact squad will be confined under guard during the time, and food brought to it.

3. In order to sun and air clothing and bedding, tents will be furled every day, weather permitting, from 8:00 A.M to 4:00 P.M..

4. The equipment and effects of meningitis patients and carriers will be sterilized, and the premises scrubbed with antiseptics.

5. Washing of hands before meals will be done under military supervision.

6. Each man will immerse his eating utensils in boiling water both before and after meals.

7. Paper napkins will be used in place of handkerchiefs and will be burned as soon as soiled.

8. Wash and boil all soiled linen at once.

9. Avoid all indoor meetings.

10. Medical officers will assemble companies in the streets and talk to them emphasizing the fact that the disease is spread by carriers by means of coughing, sneezing, spitting and the use of articles in common.

11. The following articles are often used by soldiers promiscuously: roller and hand towels, soap, brushes and combs, canteens, drinking cups, pipes, whistles, musical instruments, playing cards and dice.

12. The interchanging of clothing or sleeping upon the cots of others is forbidden.

While the above measures were regarded as being important, yet it was fully realized that the greatest hope of preventing an epidemic of meningitis lay in the detection and elimination of carriers. So far as is known, the meningococcus gains entrance to the body through the nasopharyngeal mucosæ. It escapes with the secretions and excretions from the nose and mouth. Consequently, the bacteriologic control of an epidemic centers upon these membranes.[2]

PRACTICAL DIFFICULTIES OF AN EXTENSIVE SURVEY

Theoretically, the detection of all meningococcus carriers, in a military organization of limited size is quite feasible. Practically, it is a difficult undertaking in a large army cantonment. For instance, a well-trained bacteriologist with a corps of experienced technicians and a thoroughly well equipped laboratory should be able to detect and control, with a considerable degree of accuracy, the meningococcus carriers in a unit numbering 1,000. Frequent reculturing of the entire unit is, in my opinion, essential. Suspicious or actual carriers should be isolated. Cultures should be taken from carriers daily until at least five consecutive negatives have been obtained before they return to the unit. These individuals should thereafter have cultures made at least once each week.

Swabbings should be made from the anterior nares by means of a nasal speculum and cotton-tipped applicators; also from the nasopharynx by means of West tubes. Cultures should be made in a warm room, carefully spread over warm culture plates, and placed at once in an incubator. Every known refinement in technic, from the making of culture medium to the last step in identifying organisms by well controlled agglutination tests, should be practiced. Several plates inoculated with recently isolated strains of meningococci (on account of their weak viability in contrast to that of old cultures) should be incubated with each batch of plates to serve as controls of the medium, incubation, identification of colonies, staining and agglutination. The drudgery incident to such routine and detail should never be allowed to cause relaxation of effort. Eternal vigilance under ideal conditions is the price of freedom from meningococcus carriers.

Such conditions are almost impossible to attain in a large army cantonment numbering upward of 20,000 individuals. The taking of cultures is a time-consuming process. Naturally, it interferes with the already crowded schedule of military training, which is the primary and most important function of the camp. Even with the hearty cooperation of commanding officers it is often not possible to culture an entire unit. Some members are usually on sick report, on furlough, or on special detail from which their services can not be spared. The result is that there are usually several soldiers in each company from whom cultures are not obtained, and any one of these may be a carrier. The transfer of enlisted men from one unit to another, which is unavoidable at times; also the introduction of recruits from other camps to organizations which have been cultured, make it necessary to culture "stragglers" at odd times. But in any case the system is not "air-tight."

To repeat: a large, well-trained, highly efficient laboratory force is essential to such an undertaking. Last winter it was impossible to supply such a force to each camp.

Notwithstanding these and other minor factors which militated against a perfect survey, it was decided to make the best use of all available means to culture the entire personnel of the camp, hoping thereby to eliminate most of the carriers. A contact camp was established for the isolation and treatment of carriers. The culturing of organizations, in which cases of meningitis had developed, was begun February 6, 1918, with others following as rapidly as possible.

For two good reasons it was considered advisable to take all cultures in the laboratory, rather than in the camp, as had been the practice at Camp Funston. The short distance between the camp and the hospital rendered it possible to march soldiers to the hospital with but little loss of time. The culture plates could, with greater certainty, be kept warm, and free from contamination. (The latter had always been a vexing problem in this camp on account of the sand storms.) Nasopharyngeal cultures, by means of West tubes, were taken by a medical officer with the help of a clerk and technician. In a short time, this team became very efficient so that as many as 900 cultures could be taken in a morning, although a daily average of from 500 to 600 cultures was found to be the optimum.

TECHNIC

The laboratory technic followed was essentially that laid down at the Rockefeller Institute. Veal infusion 2.5 per cent agar, adjusted to a reaction of +0.3 phenolphthalein, was prepared in large quantities, autoclaved and stored in bottles containing about 300 c.c. As many of these as were required for the day's work were melted, 20 c.c. of sterile 20 per cent dextrose solution added, and cooled to 50 degrees C. To this was added 80 c.c. of laked blood, prepared by adding 20 c.c. of defibrinated human blood to 60 c.c. of distilled water. In bulk this medium was a clear, cherry red color. From 8 to 10 c.c. quantities were poured into sterile Petri dishes, care being taken to tilt and shake the dish immediately after pouring, so that an even film of medium 2 to 3 mm. thick, covered the bottom. To insure sterility, the plates were incubated twenty-four hours before use.

During the culturing process, the plates were removed from one incubator, inoculated, labeled and immediately placed in another incubator. After twenty to twenty-four hours incubation they were examined for meningococcus colonies. Suspicious colonies were circled with a wax pencil. Where the colony was large enough a part of it was "fished," spread on a slide, stained, and examined in order to determine, at once, the Gram reaction of the organism. This could be done rapidly by placing from 16 to 24 colony-specimens on a slide in order to stain all of them at once. In this way, colonies in which no Gram-negative cocci appeared could be safely discarded. Very small colonies, and those showing Gram-negative cocci were transplanted to serum (human or horse) dextrose agar slants. After twenty-four hours' incubation, the surface of these slants was washed down with 0.8 per cent salt solution and suspension made for the agglutination tests. At this point it may be well to emphasize the observation which has been made regarding the peculiar tendency of pure meningococcic cultures to form a very fine suspension with very little agitation. Cultures of other organisms, especially cocci, required a great deal more shaking in order to get anything like a fine, even suspension. The agglutination tests were carried out in small serologic test tubes, at a temperature of 55° for twenty to twenty-four hours, using 1:50 and 1:200 dilutions of both Rockefeller polyvalent and New York State Board immune sera, and controlled by normal horse serum and salt solution. It was found very helpful in the final decision as to whether an organism was the meningococcus or not, to refer to a table in which the following points were noted: character of the colony, Gram reaction, morphology, emulsifying properties, and agglutination reaction. It is believed that many false positives were in this way avoided.

Throughout the survey, all records and data were kept by a system of dates and numbers. The date was written on the cover of the Petri dish; the numbers of the cultures on the bottom. For instance, 2/15—10 meant the tenth culture taken February 15. This culture could be identified only by reference to the roster in which was recorded the soldier's name and organization. In this way, reports were made without any reference to organization. It is interesting to note in Table I, showing the final reports by organization, the fairly uniform percentage of carriers.

TABLE I

SHOWING THE NUMBER OF CULTURES, CARRIERS, PERCENTAGE OF CARRIERS AND NUMBER OF CASES BY ORGANIZATIONS

ORGANIZATION	NUMBER OF CULTURES	NUMBER OF CARRIERS	PER CENT OF CARRIERS	TOTAL NUMBER OF CASES	NUMBER OF CASES IN FEB., 1918
133 Infantry	2,038	37	1.81	2	1
134 Infantry	2,541	33	1.29	1	1
135 Infantry	2,665	29	1.08	2	2
136 Infantry	2,921	38	1.30	3	2
125 Field Artillery	1,021	10	0.97	1	1
126 Field Artillery	1,254	10	0.79	1	1
127 Field Artillery	1,197	13	1.08	1	–
126 Machine Gun Bn.	648	10	1.54	2	2
127 Machine Gun Bn.	635	4	0.62	1	1
109 Engineer Train	583	9	1.54	–	–
109 Ammunition Train	880	12	1.36	–	–
109 Sanitary Train	793	5	0.63	1	–
109 Supply Train	244	8	3.27	1	–
109 Field Signal Bn.	408	4	0.98	–	–
Base Hospital Med. Det.	382	5	1.30	–	–
Division Stockade	103	2	1.94	–	–
Recruits	530	9	1.69	–	–
Miscellaneous, including small organizations, "stragglers," civilians, etc.	1,365	21	1.53	–	–
	20,208	259	1.28 (Average)	16	11

CARRIERS

The percentage of carriers in the total of 20,208 cultures (representing between 90 and 95 per cent of the strength of the command) was 1.28 per cent.

Carriers were sent, immediately after their detection, to the Isolation Camp, which was in charge of a medical officer, and where strict attention was given to personal and camp hygiene. Each carrier received a nasopharyngeal spray of 2 per cent dichloramine-T oil four times daily, and was sent to the laboratory every fourth day for reculturing. The carrier was allowed to return to his respective unit when three consecutive negative cultures had been obtained.

TABLE II

SHOWS THE NUMBER OF DAYS IN ISOLATION REQUIRED TO GET THREE NEGATIVE CULTURES AT FOUR-DAY INTERVALS

12 days	16 days	20 days	24 days	28 days	32 days	36 days	40 days	Over 40 days
171	18	14	4	6	7	7	4	5

The reculture records of 236 of the 259 carriers are complete. Table II shows the number of days in isolation required to get three negative cultures at four-day intervals. It does not, however, represent the actual carried period, since all carriers were held twelve days after the last positive culture. In many

instances a positive culture would be found after 1 or 2 negatives. Of a total of 1,161 cultures from the Isolation Camp, 89 or 7.6 per cent were positive, which was six times that of the camp.

CASES

As stated before, two cases of epidemic meningitis occurred in December, 1917, and three in January, 1918; two of the five terminating fatally. During February, seventeen cases were admitted to the Base Hospital with a tentative diagnosis of epidemic meningitis. In five of these the spinal fluid findings did not substantiate the diagnosis of meningitis. Of the remaining twelve, one proved to be a streptococcic meningitis following otitis media. Eleven were regarded as epidemic meningitis, and so treated, although the meningococcus was found in but eight. The organism was recovered from blood culture in one case.

Clinically, these cases as a group presented nothing very remarkable. Two were very severe, the others, if anything, rather mild. Erythematous spots were observed in but one case although carefully watched for in all. None of the cases of this series died. Regarding the ultimate military disposition, one patient was discharged from the army upon a surgeon's certificate of disability. Two others were transferred to another hospital; eight were returned to duty.

The specific treatment, to which a very great measure of the credit is due, consisted of both intraspinal and intravenous administrations of antimeningococcic serum. Both the Rockefeller polyvalent and New York State Board sera were used. Large doses were given as often as four times in twenty-four hours, although twice a day was the rule.

REPORT OF A CASE

One case is worthy of mention, chiefly on account of the complications and sequelæ which developed:

Case I. Wagoner E. L. B., 126 M. G. Bn., was admitted to the Base Hospital, February 7, 1918, complaining of general bodily aching, chills, and severe headache. Ten c.c. of clear cerebrospinal fluid, under slightly increased pressure, were withdrawn. After a long search, several Gram-negative, extracellular, diplococci were found in the centrifuged sediment. Another specimen taken the following day, was very turbid, and contained numerous pus cells and meningococci. A blood culture made the same day (February 8) revealed the same organism. The spinal fluid remained turbid until February 27, though no organisms were found after February 12.

Clinically, the case was regarded as being serious from the onset. Small erythematous spots were noted the second day. The patient was given 60 c.c. doses of antimeningococcic serum intravenously, and 30 c.c. doses intraspinally, as often as four times in twenty-four hours.

February 16, the acute symptoms of meningitis were greatly improved; recovery was expected. Suddenly on this date the patient's temperature rose; his pulse, previously slow, became rapid and very irregular; his lips and fingers were cyanotic. Altogether, his condition became more desperate than it had been at any time. A diagnosis of acute endocarditis was made, and death momentarily expected. A danger card was sent from the ward, which remained effective several weeks. During this time a bilateral convergent strabismus, which began during the first week of illness, became marked; also a partial paralysis of the right arm and leg developed.

March 1, a catheterized specimen of urine was found to contain blood, a large amount of albumin, granular casts, and a few clumps of pus cells. No bacteria were found at this time. Infarction of the kidney and ulcerative pyelonephritis were thought of, but at that time, the patient was too sick for ureteral catheterization. The bladder had to be catheterized frequently to relieve retention. Later the bladder became very irritable and would hold but two ounces of urine without overflow.

When his condition improved sufficiently, the ureters were catheterized, and specimens from both kidneys sent to the laboratory for bacteriologic examination. A direct smear of the sediment revealed many erythrocytes and small clumps of pus cells. One was surprised to find many of the latter containing as many as 5 or 6 Gram-negative diplococci strikingly similar to the meningococci. Cultures were inoculated, upon which appeared numerous soft, clear, refractile colonies, 1 to 3 millimeters in diameter. These colonies emulsified very readily in 0.8 per cent salt solution and the organisms were agglutinated by polyvalent antimeningococcic serum (Rockefeller) in dilutions up to 1:300. Type differentiation, by any of the sera on hand at the time, was unsatisfactory, although known controls at this time were not entirely satisfactory.

The patient gradually recovered the use of his arm and leg, and the strabismus improved. His general condition improved rapidly during his last three weeks in the hospital. He was discharged, upon a surgeon's certificate, July 30, after a stay of 159 days in the hospital. The case is regarded as one of meningococcic septicemia, with localization in the heart and kidneys as well as meninges.

EPIDEMIOLOGY

There are certain outstanding features bearing upon the epidemiology of cerebrospinal fever to which some reference, at least, should be made. Questions have been raised many times, relative to the influence on the spread of the disease, of climatic conditions and of lowered bodily resistance resulting from fatigue and exposure. It has been contended that cold, wet weather is a very responsible factor, and it is true that many more cases of meningitis develop during the winter and spring months than at other times of the year. The evidence against lowered resistance, a term rather loosely employed, is much less convincing. For instance, one seldom sees meningococcic meningitis as a complication or sequela of a long, wasting illness, or following general debility. It attacks, much more commonly, the apparently healthful, robust, young individual. The lowered resistance of the nasopharyngeal mucosæ due to inflammation thereof is much more likely to be a predisposing factor to infection by the meningococcus than is general bodily debility.

Although cerebrospinal fever is classed among the highly contagious diseases, and greatly feared as such, yet the development of consecutive cases does not warrant or confirm such belief. At least, as Frost[3] says, the disease "does not present the epidemiologic characteristics which we are accustomed to associate with a contagious disease. Even in carefully studied epidemics it is the exception rather than the rule to find any direct or even traceable indirect contact between cases." The latter statement applies to our efforts at Camp Cody, which were fruitless, to trace contact between cases, although it was possible in six instances to establish the probability of fairly direct contact between cases and carriers.

A full authoritative discussion of these important questions requires reference to more medical literature than I have access to, at present, and is hardly within the province of this report. It will be sufficient to indicate their application particularly to this camp.

Expressed briefly, climatic conditions at Camp Cody may be summed up in the words "high and dry." The altitude is approximately 4,500 feet, and an hour rain or snowfall during the winter or spring seldom occurs. The winter nights are noticeably cold, though the thermometer seldom registers below zero, F. The sun shines brightly nearly every day. Violent sand storms, sometimes lasting a day, or several days, are very prevalent during the winter and spring

months, and, as stated previously, were undoubtedly the cause of a great deal of nasopharyngitis.

In order to bring out the true relationship of the latter to the incidence of meningitis it should be stated that the sand storms were no more prevalent in February—the month in which the greatest number of cases occurred, than in March, April and May during which time but one case developed. Eighty per cent of the meningococcus carriers which were found, however, were under quarantine by the middle of March.

The element of fatigue was probably of neither greater nor less importance at this camp than at others. Exposure to wet, cold weather was probably very much less here than at other camps in the same latitude and north of it. The daily average mean temperature as furnished by the U. S. Weather Bureau for Deming was 40.6° in January, 53.2° in February, 55.4° in March, and 60.1° in April.

On the whole, the general health at this camp was not far from the average when compared with other camps. With an annual death rate of 12.7 per 1,000 for the six months ending March, 29, 1918, it stood a little lower than midway between the highest, Camp Wheeler, 28.3 and the lowest, Camp Dix, 2.9[1]. Regarding the seasonal occurrence of infectious diseases, the situation may be summarized as follows: an epidemic of measles began early in November, 1917, reaching its high point the week ending December 7. Associated with, and following this epidemic there developed, within the next 45 days many cases of bronchopneumonia. The incidence of primary pneumonias increased rapidly in January, reaching a climax in February. More cases of scarlet fever, mumps and diphtheria occurred during January, February, and March than in any other equal period of time. In fact there was a definite, decided culmination of all the more common infectious diseases during the latter part of January and February, which was also the period of the largest number of cases of cerebrospinal fever. This observation is in keeping with a deduction which Woolley[4] has made, that since "the incidence of meningitis and that of the commoner respiratory diseases are parallel; if, in fact, the appearance of meningitis follows the rise in acute respiratory disease, then one may quite reasonably draw the inference that there is some definite connection between the two." There is reason for believing that the primary infection in all develops in the respiratory tract, and more particularly, the nasopharynx. It is held that meningitis is primarily a nasopharyngitis, the infecting agent gaining access to the meninges either by direct lymphatic extension, or the result of a septicemia, with localization in the membranes of the cord and brain.

There is one element, however, which must be kept in mind. No combination of predisposing causes will give rise to epidemic meningitis without the presence of the meningococcus. Upon a moment's reflection this statement becomes obviously true. Fatigue, exposure to inclement weather, and the existence of a nonspecific nasopharyngitis are highly important, practical factors to be considered in the epidemiology of cerebrospinal fever. Yet, the one necessary element is the meningococcus, and since this organism soon perishes when once it is separated from its natural habitat—the nasopharynx—the problem of its dissemination resolves itself into that of the active meningococcus carrier.

In camp life, the various elements such as close personal association, fatigue and exposure, which unite to pave the way for nasopharyngeal inflammation, can not well be overcome. The other link in the chain, the elimination of carriers, can be broken, and herein lies the rationale of a survey for meningococcus carriers.

It is too much to expect that all carriers in a large cantonment will be found in a single, or, even in repeated surveys. It may be argued that, where only sporadic cases develop, the time, labor and expense involved in such a survey, together with the uncertainty of results, will not justify the taking of such measures. On the other hand, it can not be foretold in the beginning whether cases will develop sporadically or epidemically. Since the aim of a survey is to prevent the latter happening, it should, when circumstances permit, be undertaken very soon after recruits are assembled. This recommendation applies especially in instances where troops are being mobilized from sections of the country in which cerebrospinal fever is endemic. The meningitis epidemics at Camp Funston, and Camp Jackson, have been attributed very largely to the endemity of the disease in Missouri and Kansas, and in South Carolina, respectively. It should be stated here that troops composing the 34th Division which was stationed at Camp Cody, during the winter and spring of 1918, were from the National Guard organizations of Iowa, Minnesota, Nebraska, and South Dakota.

Meningitis is a serious disease by reason of its high fatality, and the disabling sequelæ which are apt to follow it. It has been estimated to be 45 times as prevalent in the army as in civil life, whereas the figure given for measles is 19, and for pneumonia 12[1]. Therefore, it would seem that strenouous measures should be taken against the introduction and spread of this disease, within army camps.

COMMENTARY

Regarding the incidence of the disease in relation to the culturing of this camp for carriers, it is noteworthy that the last case of the series (in point of time) developed February 23, 1918, in a soldier who was a carrier in the Isolation Camp. By this date all companies in which cerebrospinal fever had developed had been cultured and many carriers quarantined in the Isolation Camp under treatment. Whether these two facts stand in anything more than coincidental relationship, it is difficult to say. Only one other case of meningococcic meningitis occurred in the 34th Division before that division left this camp in September. This case developed April 23. Curiously, this patient was admitted to one of the pneumonia wards with a tentative diagnosis of pneumonia. A blood culture made the following day (but after a clinical diagnosis of meningitis had been made) revealed the meningococcus.

During the course of the survey several questions of both practical and scientific interest quite naturally suggested themselves. It would have been interesting to reculture a number of organizations in order to ascertain what proportion of carriers had been missed in the first culture or whether new carriers had appeared. This was done in but one instance, which was occasioned by the development of a case of meningitis in the 126th Machine Gun Battalion thirty-eight days after that organization had been cultured. Nine carriers were found

the first time; two were found the second time, one of whom had been picked up in the first culture. This soldier had been in the Isolation Camp twenty-four days, during which time two positive and three negative cultures were obtained from him. The latter released him from quarantine although the subsequent positive culture would point to the probability of his not being entirely free from meningococci in spite of three negative cultures. No other cases of epidemic meningitis developed in organizations which had been cultured previously.

An investigation regarding the efficacy of the treatment of carriers was proposed, but the stress of work devolving upon the laboratory at this time precluded the undertaking of the purely experimental work involved in this problem. As stated before we relied solely upon the use of a 2 per cent dichloramine-T solution in oil, administered in the form of a nasopharyngeal spray, to artificially hasten the disappearance of meningococci from carriers.

It was reported at Camp Funston that this spray, induced hyperemia about the orifice of the eustachian tube followed by the development of cases of otitis media. At Camp Cody no untoward results were observed from this source.

SUMMARY AND CONCLUSIONS

1. It is a safe prediction that cases of epidemic meningitis will develop wherever large numbers of recruits are assembled and live together for any considerable length of time, in close quarters. The intimate personal associations, unavoidable in camp life greatly favor the dissemination of the disease; hence, the potentiality of a serious widespread epidemic.

2. The dissemination of cerebrospinal fever depends ultimately upon the presence of meningococcus carriers, although the existence of a nonspecific nasopharyngitis is undoubtedly a predisposing factor in the development of the individual case.

3. The period of greatest incidence of meningitis may be expected when the more common respiratory infections are at their height, due to the fact that in all of them, nasopharyngitis is a primary and predisposing factor. The greatest number of cases of the latter develop when living conditions are at their worst.

4. In military camps, where large numbers of troops are mobilized from sections of the country in which meningitis is endemic, the possibility of the disease becoming epidemic is greatly increased, by reason of the greater proportion of meningococcus carriers. A determined effort should be made, in such instances, to eliminate the carriers as quickly and thoroughly as possible. A general bacteriologic survey is the only logical means to such an end, and although its accomplishment on the large scale necessary in the average camp is fraught with many practical difficulties, it should be undertaken.

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THE ROLE OF TUBERCULOSIS IN DEMENTIA PRECOX*

(Second Report)

By H. I. Gosline, M.D., Worcester, Mass.

THE following report is intended to supplement the Preliminary Study† of the same title and is the extended account of the seventeen cases mentioned there, in which the connection between the mental and the physical disease was so close that certain writers have considered the one as due to the other.

The history of the case which may be considered to serve as a type for the other seventeen cases and which will have occurred in the experience of every psychiatrist, is as follows:[1] A girl of 27, of tuberculous build and who has shown signs of latent tuberculosis, remains depressed and introspective following some disappointments. There appear difficulties of attention, cerebral torpor, absent-minded periods, then transitory ideas of persecution and feelings of hatred against her parents.

After several weeks there follows a melancholic state with stereotyped writing.

Soon after there suddenly appear catatonic manifestations: prolonged immobility, negativism, cerea flexibilitas, cataleptoid attitudes, stereotyped movements, suggestibility. A slight remission was observed during the next few months but the automatic manner and the stereotypies were maintained. The mental condition is slightly affected in spite of appearances; no confusion, no disorientation, conservation of the feelings of hatred against her parents and of the sense of shame.

Admitted following the remission. Fixed positions and catatonic phenomena resumed. Progressive cachexia. From time to time a slight febrile reaction is noted, with headache and epistaxis associated with a tuberculous infection which is developing at the apices of both lungs.

The autopsy showed that we were dealing with a case of fibrocavernous tuberculosis. A study of the organs and of the glands of internal secretion revealed nothing abnormal. In the nervous system was seen a sclerous meningitis with small hemorrhages, in various stages of evolution, and distention of the arachnoid spaces with edema. The examination of the cortex, etc.

The study of the clinical symptoms and the anatomic findings leads the authors to decide upon the diagnosis of melancholia with stupor of dementia precox, in spite of the existence of the catatonic syndrome. They are of the opinion that this agrees with the conception of Regis and certain other authors who think that intermediary forms exist between certain forms of chronic mental confusion of toxic-infectious origin and dementia precox.

There is opportunity to mark out the domain of this psychosis, with the aid of carefully compiled clinico-anatomic data. The syndrome of Kraepelin seems to be realized by two types of psychosis: the one which is really worthy

*From the Laboratory of the Worcester State Hospital, Worcester, Mass.

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of the name dementia precox, is a constitutional psychosis, following puberty independently of toxic or infectious causes.

The other type would be a form of toxic-infectious psychosis, often of tuberculous origin, which would take the form of dementia precox but would not always lead to dementia and would be curable in the cases in which the meningeal and encephalitic lesions were not pronounced and were halted in their course. The future will tell whether such a division, interesting from the point of view of prognosis, is justified by the discovery of symptoms and of lesions characterizing the two varieties of the hebephrenocatatonic syndrome.

Following the plan in the previous paper, the tabular view form of presentation is adopted. The cases are as follows:*

As was pointed out in the first paper, we are dealing with a special, selected group of cases. These cases were selected because they were undoubted cases of dementia precox; all of them could be placed in the catatonic group or the hebephrenocatatonic group, as some writers would have it. With the whole material now before us there will be some doubt expressed as to the grouping. Were they really cases of dementia precox? In the discussion which followed the reading of the French paper it was claimed that the case was not one of dementia precox because the affectivity was preserved, "the patient showed animosity and affection for certain individuals till the end." This was considered prima facie evidence against dementia precox. The question might be raised as to whether even this retention of the affectivity would have had weight before death in making the diagnosis against dementia precox in face of the negativism, cerea, and stereotyped movements which the patient displayed.

In our group of seventeen cases there are some even more clean-cut cases of dementia precox, in which the question might be raised with all the material now before us. A review of the cases shows three main groups: the agitated depressed, the apathetic stupor, the hysteriform. There is a poorly defined mixed group in which agitation and apathy combine or alternate. To the first group belong Cases III-6, III-24, XVI-23, XVII-43, 14-7. Related but without the depression are Cases IV-16, IV-18, V-3. To the second group belong Cases III-14, 1916.25. To the third group belong Cases III-31 (agitated), VII-41 (agitated depression). To the mixed group belong Cases XII-28, (agitated stupor), XIII-17 (agitated apathy). Two cases (III-43, VIII-3) were first agitated and later apathetic, and one case (IV-8) was first stupid and later active. If we were to place the French type case in one of these groups, we would be safe in considering it one of hysteria, major form, though the cardinal signs are absent. The stereotypies and attitudes might equally well be hysterical or catatonic as far as the presentation of the case is concerned.

The terms used to describe these groups, while more or less generally discarded like melancholia attonita, still may serve to convey the total effect of a case upon the observer and as so used may still have some value. Using them in this way we have three main groups and these are the groups so frequently associated with infections other than tuberculosis. If we consider our cases of dementia precox in this way, may we not arrive at a differentiation of the two

*Signs have the same meaning as in previous paper. Numbers after symptoms or signs refer to number of days of month each was present.

Case III-6

MENTAL

1896—Onset with depression and agitation. Auditory hallucinations, delusions of persecution and of poisoning. Tube fed. Assumed fixed standing positions. Spent night on knees, praying in the coldest weather. Fear affect.

1897, March—Negativistic, resistive, tube fed April—Delusions of poisoning. Cries but stops at once. Stares, practically mute. May—Aggressive. June—Eats voluntarily but secretly. Says his "stomach is broken." Stands like a statue with head bent and resists being moved. August—Explains his financial troubles. October—Tube feeding again for 10 days.

CONDUCT CHART	
Year, 1897	
Month, 10	
NOISY	×
TUBE FED	±
SLEEP POOR	+
APPETITE POOR	×
ILL	×
UNTIDY	×

PHYSICAL

Anemic, bad capillary circulation, obstinate constipation, foul breath, insomnia.

1897, April—Spits. Five feet, ten inches tall, weighs 180 pounds. Rigid muscles.

October—Continued pyrexia. Rales both lungs. Prolonged expiration upper lobes.

November—Emaciation, pain in both chests low. Fetor and when on left side, cough with foul expectoration. Exit.

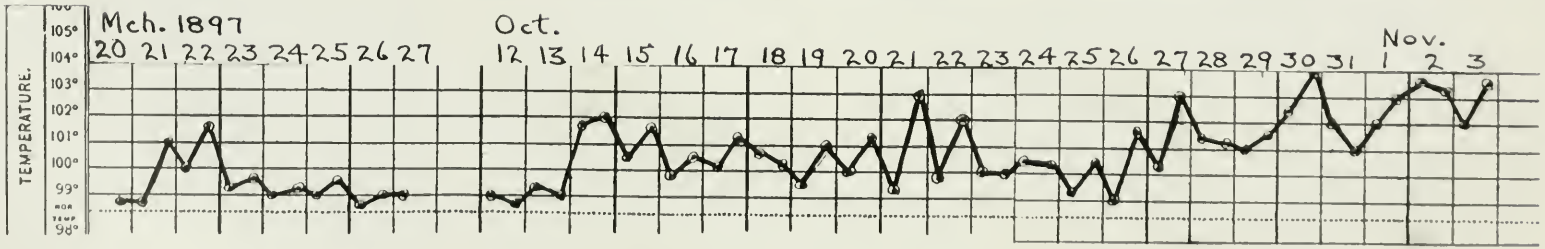
SUMMARY

Patient, age 29 or 46 (error in dates), has physical signs often found in tuberculosis and develops an acute catatonic condition which continues till death two years later. Two months before death active clinical tuberculosis develops.

Autopsy reveals adhesions posteriorly over right lung and at apex of left. Right lung consolidated, most marked at anterior, inferior, and interior portions. Firm, light, reddish gray, with rough, uneven feel at apex where it is nodular. Middle lobe shows abscess. Wt. 1227 gm.

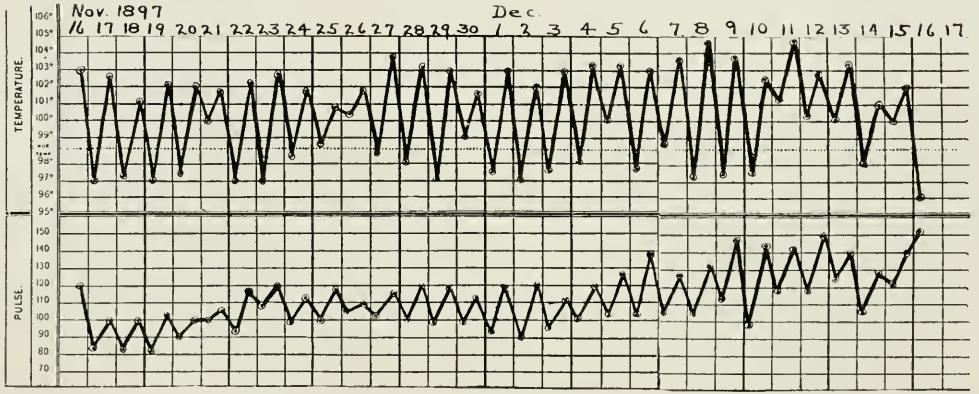
Left upper lobe seat of small hard nodules of slate gray color, most at apex. Consolidation posterior border. Lower lobe shows gangrenous cavity and is consolidated, except the anterior border. Color pinkish gray with opaque gray, marble-like areas. Wt. 1048 gm.

Over pons, beneath basilar artery is an extravasation into pia, jelly-like, resembling tapioca.



CASE III-14

MENTAL	PHYSICAL	SUMMARY
From the age of 10 different from other boys. 1892—Change of character. 1895—Everyone dominates him, no self-control, can not think. Dull, morose, reserved, "temper." Facial mannerism. 1896—Careless, stupid, silly, cerea. 1897—Sits in one position for long periods. Tube fed, irrelevant, incoherent, orientation for time poor, remote memory poor, no insight. Apathetic stupor.	Masturbated since 6 years of age. 1895—Speech hesitant. 1896—In bed. 1897—Loss of appetite. Emaciation. November—Percussion flat at inferior angle of right scapula, respiratory sounds absent. Same left side and friction rub over left lower lobe anteriorly. Hyperresonance elsewhere. December—Exit.	Gradual change in an abnormal individual. Active physical signs noted one year after active mental symptoms begin. Come to examiner's attention one month before death. Autopsy—Intestines distended. Adhesions through left chest except outer surface lower lobe. Cavity at apex. Right lung 1180 gm. Consolidation of upper lobe except apex and lower lobe except inferior parts and edges; partial consolidation of middle lobe. Many caseated cavities in upper lobe, tubercles in middle and lower lobes. Left lung 1240 gm. Lower part of lower lobe crepitant. Upper lobe solid with many cavities. Lower lobe many tubercles. Two accessory spleens.



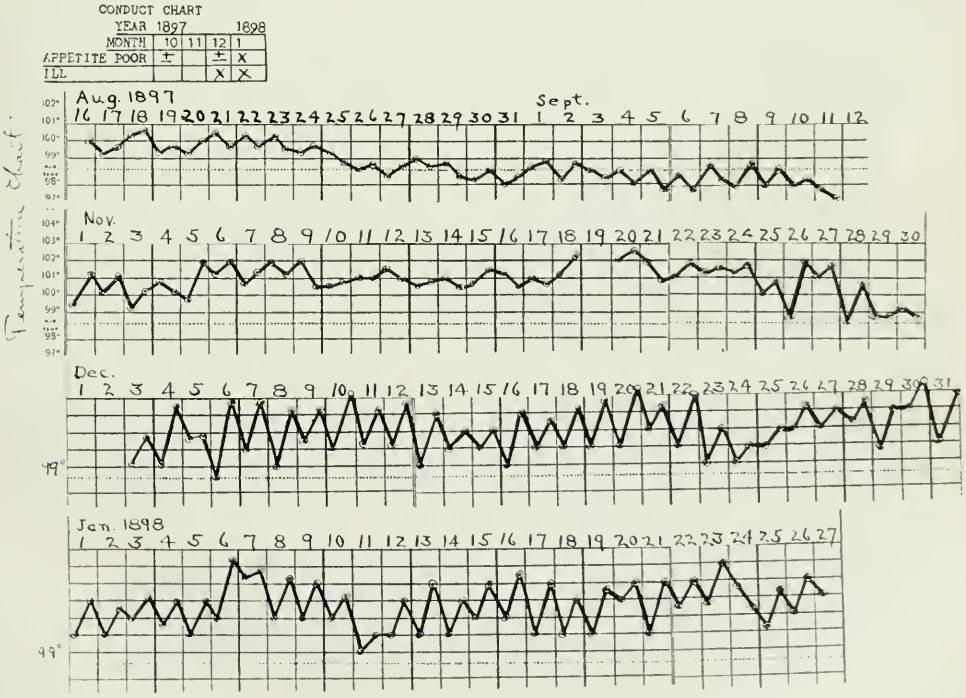
CONDUCT CHART

YEAR 1897

	MONTH 10	11	12
UNTIDY	X	±	
APPETITE POOR	±	±	±
ILL	X	X	X

CASE III-24

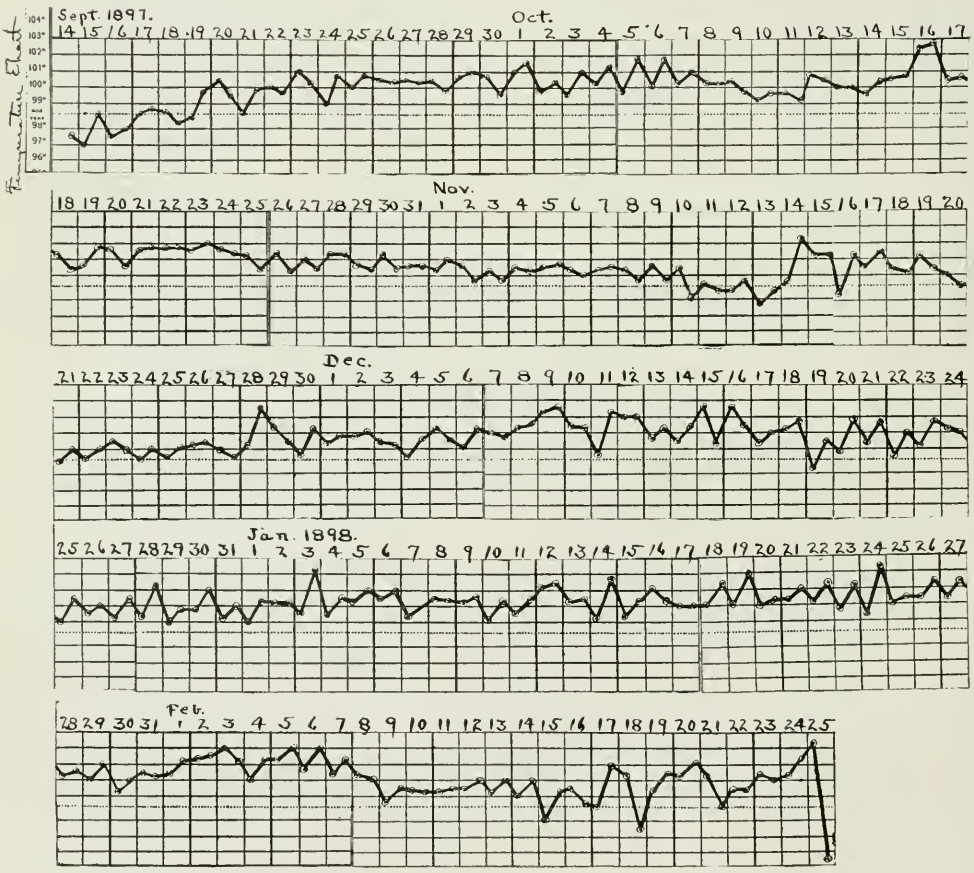
MENTAL	PHYSICAL	SUMMARY
1897—Depressed, somewhat excited. Auditory and visual hallucinations. Hesitates and repeats answers. Points to heaven. Throws head to right forcibly. Prays, grimaces, walks about house, will not address wife. Thinks Catholics will shoot him. Disoriented for time. "Medicine is pumped up from sink." Mute at times. Sexual delusions. Confused, incoherent. Stereotyped movements and attitudes. Destructive at times. October—Shows some insight. November—mannerisms. December—Does not know why he is mute.	1897—Health failing gradually. Insomnia. August—Pain in chest, white foaming sputum. September—Sudamina forehead, temples and chin. Sebaceous scales. November—Says he "spits and bleeds and aches in his chest." December—Flat right apex and subclavicular region. Percussion causes cough. Dullness posteriorly throughout, more at apex and interscapular border. Bronchial breathing apex and scapular border. Rales in second space. 1898, January—Cough and bloody expectoration on passing tube for feeding. Other hemorrhages later. Catheterized. Exit.	Failure in physical health and development of tuberculosis runs parallel with the mental symptoms. Total duration less than two years. Autopsy—Bladder to umbilicus. Intestines distended. Mesenteric glands enlarged and nodular. Right lung, wt. 1415 gm. Cavity size of an orange at apex, others throughout lung. Upper and middle lobes consolidated. Numerous tubercles about bronchi, lower lobe. Left lung, wt. 673 gm. Adherent throughout. Upper lobe consolidated with numerous caseated cavities. Similar areas at anterior margin of lower lobe. Accessory spleen.



CASE III-31

CONDUCT CHART

YEAR	1897			1898	
MONTH	10	11	12	1	2
EXCITED	±				
NOISY	±	±	X	X	±
RESTLESS		X	X	X	X
UNTIDY	X	X	X	X	X
TUBE FED	X	±	X	X	X
SLEEP POOR	±	±	±	±	X
APPETITE POOR	X	X	X	X	X
ILL	X	X	X	X	X



(See Table, page 403)

CASE III-31

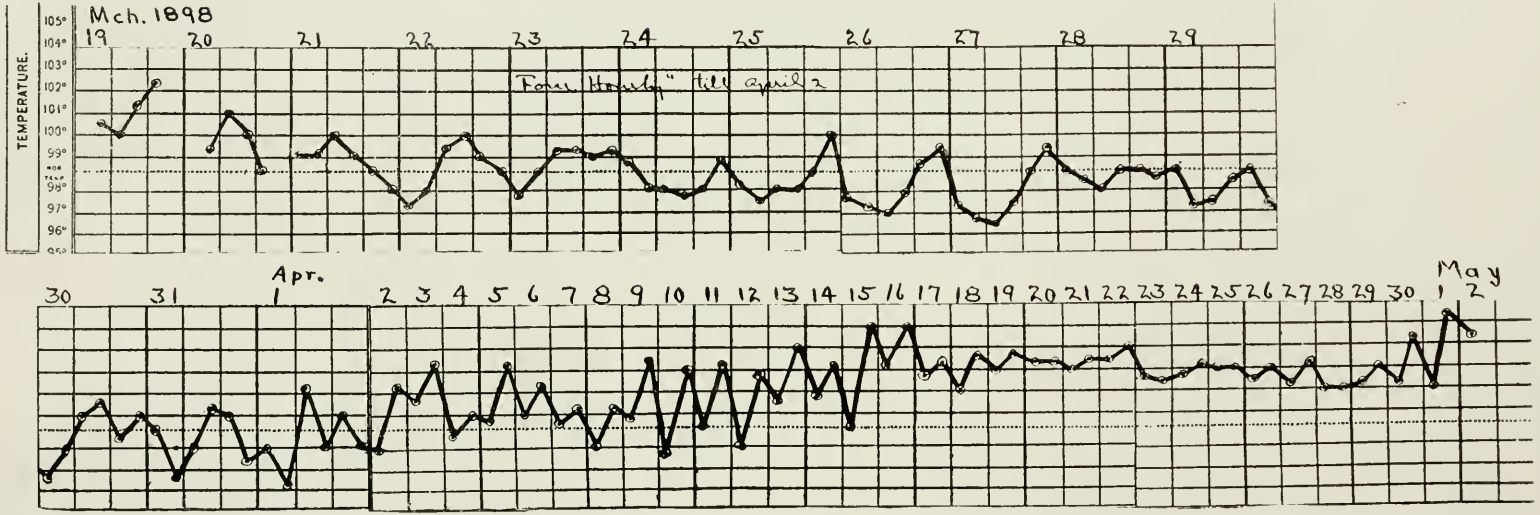
MENTAL	PHYSICAL	SUMMARY
1897—Saw caterpillars and animals on the wall at times, refused food, talked incoherently and loudly, mumbled and stared. Auditory hallucinations, violent, threatening, feared she would be burned up. Said people hit her and wanted the bumps examined. Felt exalted in her religion. Thought her limbs were gone and that it was done by electricity. Disoriented. At first said her trouble was in her brain. Answered promptly but irrelevantly at times. Restless and once held a fixed position. September—Thinks she is not at home when she is. Thinks clothes are on fire. Insolent, lewd, profane, tries to leave house unclad, screams. Sept. 21—Grasps at objects near, people, bedclothes, etc. Staring, forehead wrinkled. Says, "I don't know how, where." Affect of fear. Mutters low and unintelligibly. Moves arms about in purposeless manner. Becomes more stupid, drools, untidy, tube fed, holds food in mouth till it runs out. Disoriented, smiles in silly manner. Sang at night, smiled once at joke, moves lips. Questioned, laughs quietly, then cries without tears. Sept. 30—Noisy when moved. October—Catatonic, irrelevant. November—Delusion of negation, untidy, says she is insane. 1898, January — Oriented and calls nurses by name. "At times does not see people well and does not know them." Thinks she lost a foot and wishes physician would see. February—Threatens suicide.	Father and uncle nervous. Maternal uncle "foolish" after scarlet fever. Two paternal aunts and brother died of tuberculosis. Paternal uncle and brother died of cancer. Three children nervous, two miscarriages. Semi-invalid after birth of first child at 26 or 28. Would wake up choking last two years. 1896—Would become rigid but had no convulsions, called "spasm." 1897—"Spasms" sometimes preceded by a scream, lasted 1 to 2 minutes. Insomnia, poor nutrition, poor muscular tone, face flushed, extremities cold and anemic, feels exhausted. Urine shows s. p. t. albumin. Sept. 21—Skin of mouth and forehead scaly. Sept. 30—Pharynx congested. October—Diarrhea, tongue coated, scales at corners of mouth. November—Decubiti, emaciation, cough with expectoration. December—Rales anteriorly and dullness posteriorly on right. Sputum negative. 1898—February—Arms, legs, and feet swollen. Death.	Patient a semi-invalid for some time and with a strong hereditary taint, goes into a confused, muttering, delirious state with catatonic features. The physical condition rapidly becomes poor and ends with signs of tuberculosis. Autopsy—Decubiti. Petechiæ over abdomen and chest. Extensive adhesions right, few over left lung. Right lung indurated with large nodes made up of "slightly confluent tubercles of caseous decay." A few cavities appear at the apex. Left lung shows nodules in posterior and middle parts of upper lobe and in lower part of lower lobe. Many confluent groups of tubercles appear on section.

(See Chart, page 402)

CASE III-43

CONDUCT CHART
YEAR 1898

MONTH	3	4
UNTIDY		±
ILL	±	×



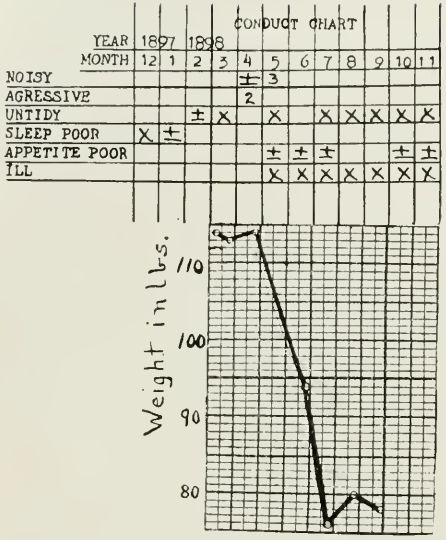
(See Table, page 405)

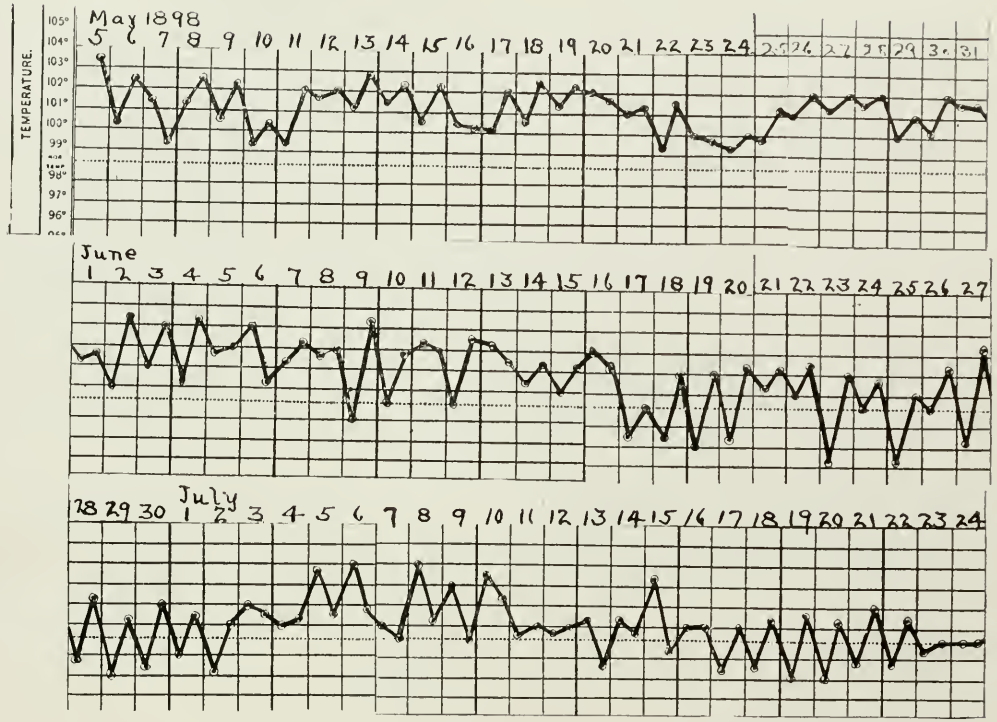
Case III-43

MENTAL	PHYSICAL	SUMMARY
Always reticent. Six months before active onset said "peculiar things" and had buzzing in the ears. Two weeks ago affect of fear. Delusions of persecution, suicidal attempt, violent, dangerous. 1896, January—Hallucinated, restless, dazed, confused, incoherent, suspicious. February—Improves. June—Dull and apathetic. July—Irritable. October—Threatening, masturbates, sits in one position all day. 1897, May—Dull, unoccupied. June—Mannerisms. September—Talks to self, untidy. 1898, January—Indifferent. April—Mute, will not open eyes.	First lost weight. 1896, July—Began to gain weight. 1898—March—Weak, mitral murmur, legs swollen. Bubbling rales left lung, friction rub, dullness. Cough, temperature, t. b. abundant. April—Knees have gradually flexed. Right hand paralyzed in flexion. Epistaxis. May—Death in stupor.	Gradual onset with dazed, confused attitude, followed by improvement and relapse. Initial loss of weight, then a gain, and finally dementia precox, contractures and positive sputum. Autopsy—Right lung shows small nodules. Left lung adherent throughout. Contains hard nodules, infiltrated foci, and some caseated and abscess areas. Nodules in left kidney and in liver.

(See Chart, page 404)

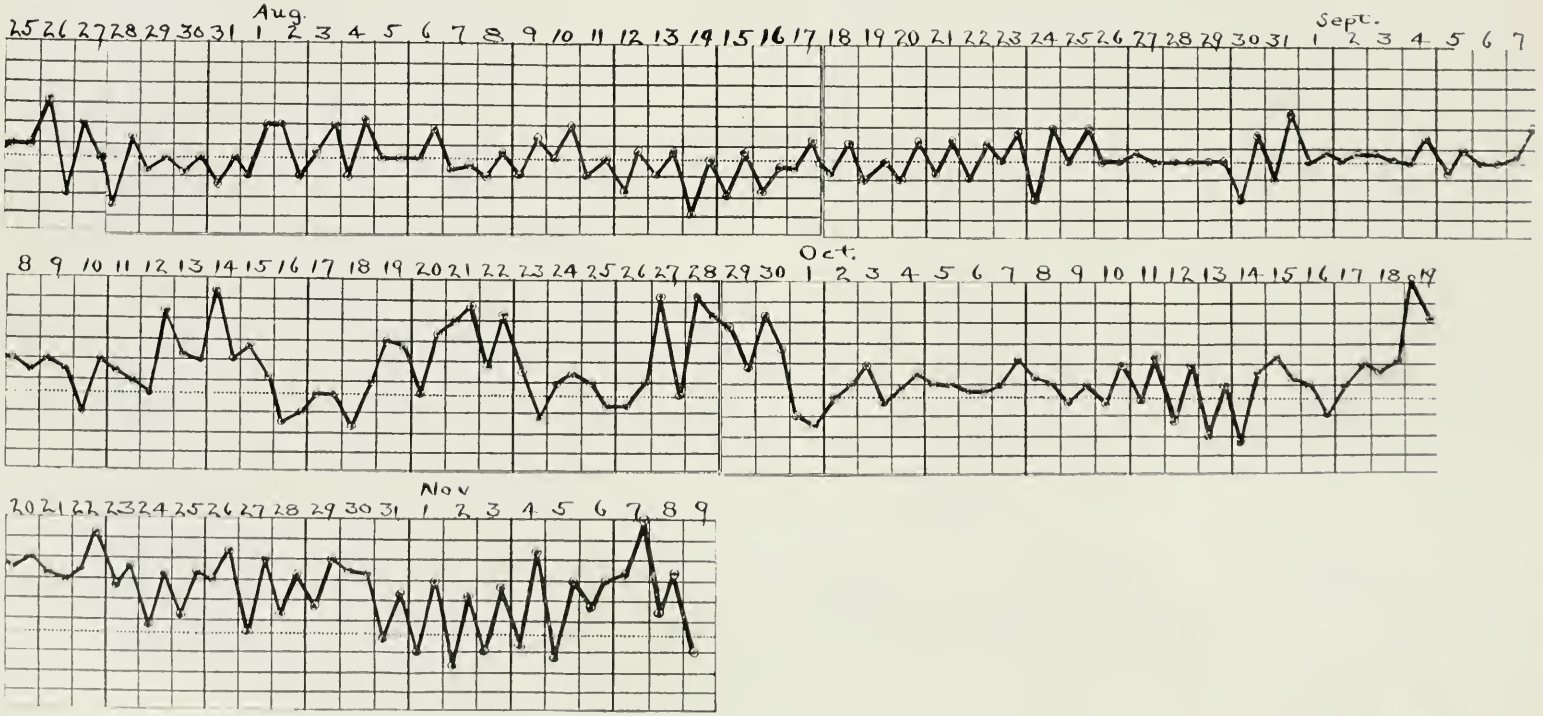
CASE IV-8





(See Table, page 408)

CASE IV-8—Cont'd



(See Table, page 408)

CASE IV-8

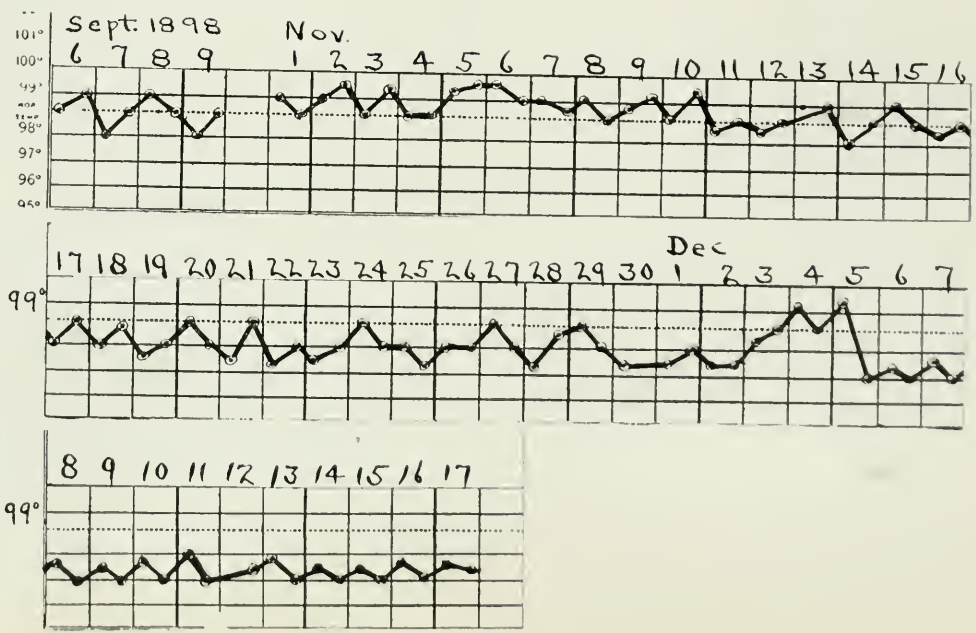
MENTAL	PHYSICAL	SUMMARY
Over a year ago thought meat bad for the head. 1897, January—Washes oftener than usual. Saw a cat on two legs like a man and heard devils cursing him and saying they would get hold of him. March—Would sleep in chair at dinner, stupid and staggered on rising. Delusions that enemies were trying to poison him. Confused, replies uncertain, memory defective. "Puzzled in mind, kind of dreaming." Sexual ideas, irrelevant. April—Muscular rigidity. May—Dribbles saliva, refuses food, mute, stereotyped movements. Insight, none. July—Aggressive. September—Untidy. 1898, May—Thinks he has died and is different. The world has come to an end. Irrelevant, incoherent. A young woman comes to him in spirit.	Has masturbated since the age of 10. 1897, January — Insomnia. April—Acne arms and back. Knee jerks exaggerated, arms rigid, tremor of hands and tongue. December—Mitral murmur. 1898, May—(?) pneumonia right upper lobe and nephritis. Later sweats and tuberculous temperature. August—Sputum positive. October—Decubiti, weak. November—Exit.	Onset with active mental symptoms which soon lead to a confused, stuporous existence. Signs of active pulmonary disease noted first over a year after mental trouble began. Autopsy—One liter of fluid in chest. Right lung adherent throughout. Gray nodules present and confluent areas with caseous lumps. Left lung, adherent upper lobe, lobe nodular. In lower part are many cavities with slimy pus and gray gelatinous nodules in hardened tissue.

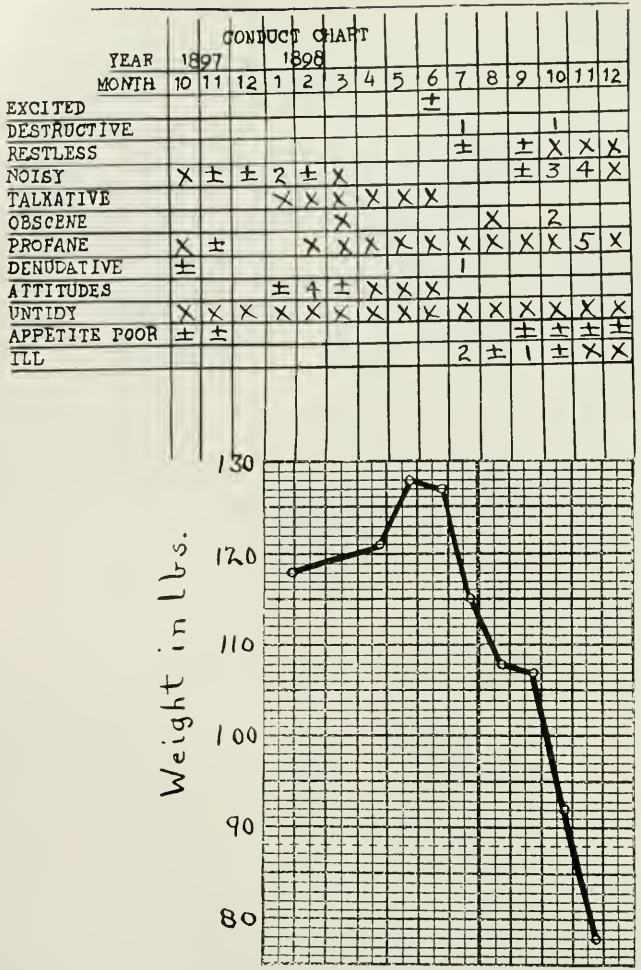
(See Chart, pages 406 and 407.)

MENTAL	PHYSICAL	SUMMARY
1898, August—Hysterical laughing and crying. Suspicious. September—Excited at times. "Policemen are hunting her on the street." At times violent, excited and destructive, then confused, dull and untidy. On admission was irrelevant, incoherent. Had a "wild stare," moans, holds lips firmly together, negativistic, pulls her hair out, removes her clothing, is resistive, restless, tube fed. October—Stiffens her body when fed. November—Screams. (?) thinks some one is in her room.	One sister said to be similarly affected. September—hyperhidrosis. Later "cheeks more sunken." October—Epistaxis. Pregnant. November—Child born. Knee jerks exaggerated. December—Decubiti, weak, emaciated. Exit.	A mixed active and dull confused state with catatonic symptoms and terminal fear affect. Physical picture clouded by pregnancy but final signs. Autopsy—Right lung firmly adherent anteriorly and posteriorly. Nodules at apex and in lower lobe. Left lung the seat of nodules of egg size to pea size, firm or slightly soft. Bronchial glands enlarged.

CONDUCT CHART
YEAR 1898

MONTH	9	10	11	12
EXCITED	X	X		X
RESTLESS	X	X		X
NOISY	±			±
IRRITABLE	Z	X		
AGGRESSIVE	Z			
RESISTIVE				X
DENUDATIVE	X	X		
UNTIDY	X	X	X	X
SLEEP POOR	X	±	X	X
APPETITE POOR	X	X	X	X
ILL		±	X	X

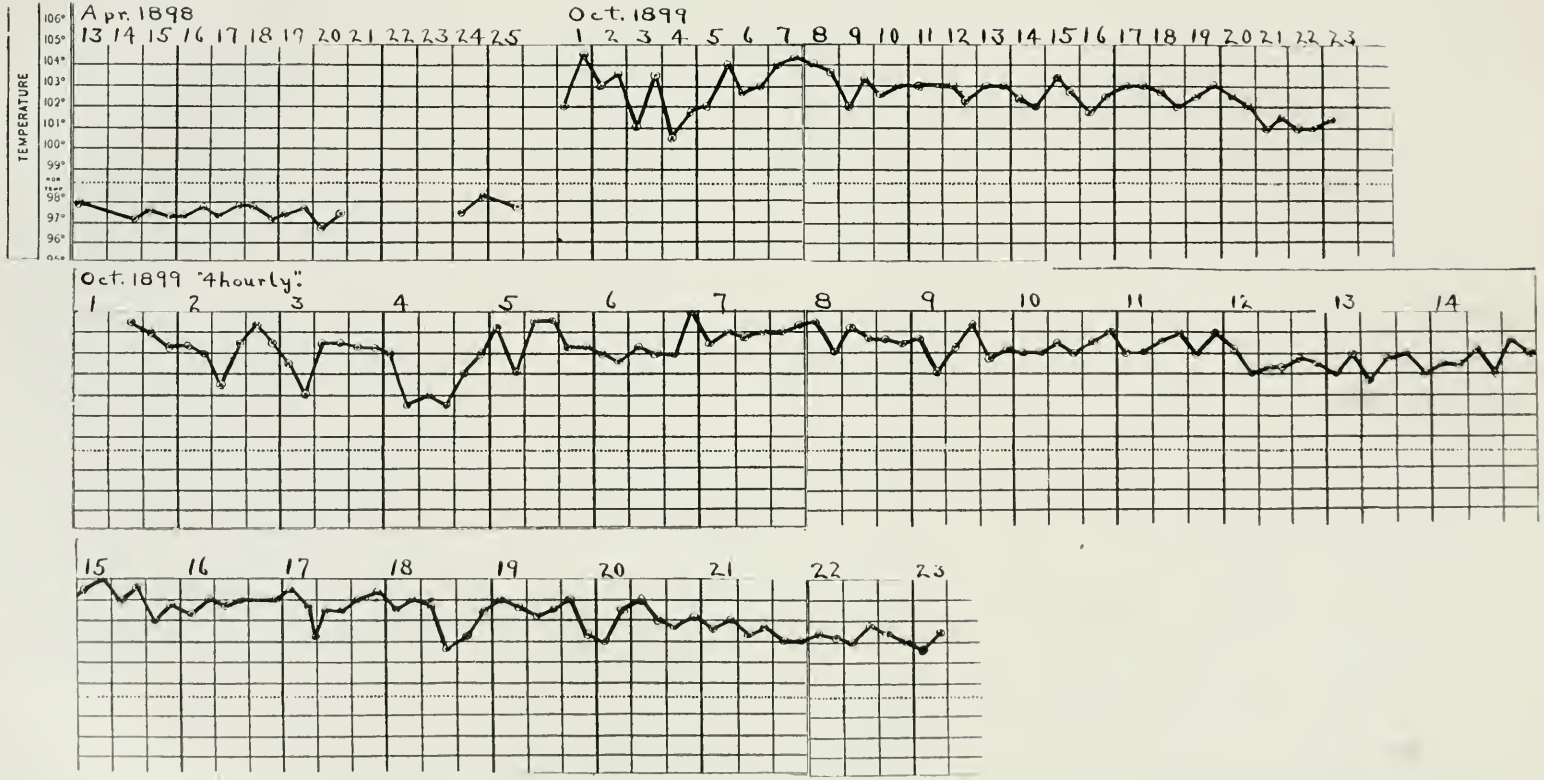




Case IV-18

MENTAL	PHYSICAL	SUMMARY
1897, January—Christ and the Virgin appeared to him. February — Peculiar actions, spitting, answering employer or not as he liked, walked around a building six times, etc. March—Sexual ideas, irrelevant. Spits and talks over his right shoulder "because he tells the truth to the right." God wants him to go through these "performances." Stereotyped positions, movements and expressions, cerea, disoriented for time. Answers after long pause. Mutters a word salad. Says words "that surprise himself," neologisms (pidginess). May-June—Rubs head with handkerchief, "a snail is in his head and in his finger." October—Becomes untidy. 1898, January—Cerea, stereotypies, gesticulates, attitudinizes. February—Silly, uncontrolled laughter, incoherent, irrelevant, sometimes mute, noisy, violent.	Probably illegitimate child, masturbates occasionally. 1897, March — Pain sense impaired, skin can be pierced without patient flinching. 1898, July-August — Feet swollen, mitral murmur. December — Only recorded temperature 97.6°. Left apex flat, loss of weight, cachexia, bolts his food. Later dry rales. Exit.	Sudden onset at 22 years with catatonic symptoms which soon lead to complete disorder of conduct and thought connections. Early impairment of the pain sense and late evidence of tuberculosis. Autopsy — Decubiti. Right lung adherent at apex, left pleura obliterated throughout. Left upper lobe indurated, some hemorrhage present and some small yellow nodules.

CASE V-3



(See Table and Charts, page 412.)

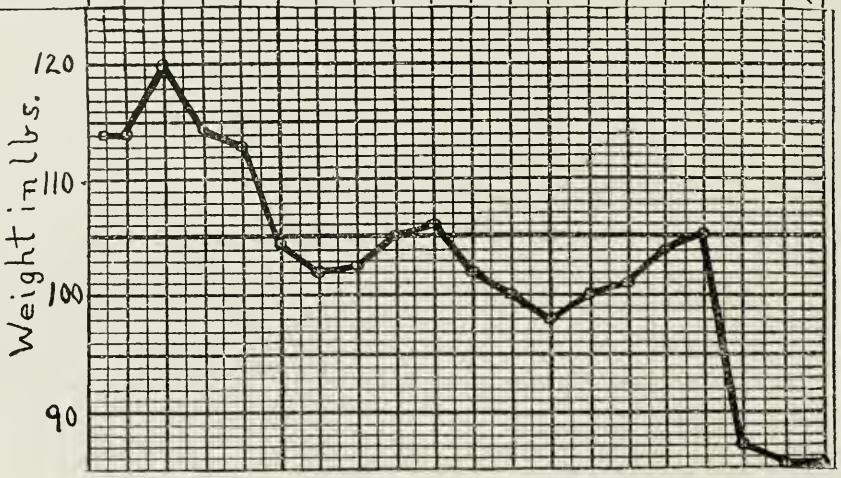
Case V-3

MENTAL	PHYSICAL	SUMMARY
1897, May—Talked and worried about the future. June—Silly laughter, claims that she sees a man who wants to talk to her. Later "spells of crying." Took a vacation during which she attempted suicide twice. September—Irrelevant, "as bad as ever." 1898, February—Since September alternate improvement and relapse. Now thinks she can communicate with people on the street. Will talk and then stop as if listening. Said her father paid the doctors to keep her in the condition she was in. "They would do better to get her a young man." Violent, untidy, talked love, had to be dressed. April—Impulsive, decorates, poses, auditory hallucinations, restless, erotic, will not help herself, oriented. May—Resistive. July—Irrelevant, incoherent, silly. August—Shakes body, obscene, aggressive. September—Untidy, helpless and aggressive. October—Masturbates. November—Fixed attitudes, horror of bathing. Condition similar for the next year.	Maternal aunt and mother insane. 1897, May—Loses flesh. 1898, April — Papular eruption on face, forehead, back, chest and arms (acne vulgaris). Comedones on cheeks. 1899, October — Pneumonia. Later, sputum positive. Exit.	Mental symptoms come on gradually at 23 years. There is a continuously active sexual trend with deterioration in one year and death in less than two years. At the beginning there is a loss of weight and after admission to the hospital a continuous loss but no determined diagnosis till the last month of life. Autopsy—50 c.c. blood-stained fluid in each chest. Old, firm adhesions both lungs, left upper lobe anteriorly and laterally and posteriorly at the apex. Right lung, lower part of upper lobe consolidated, middle part shows numerous clusters of nodules, lower lobes less numerous nodules. Left lung, numerous cavities upper lobe, one 4x6 cm., lower lobe studded with small nodules.

(See Chart, page 411.)

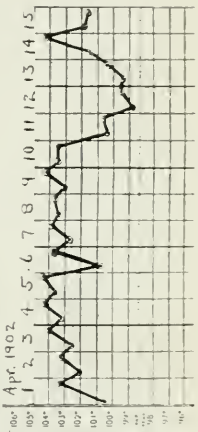
CONDUCT CHART

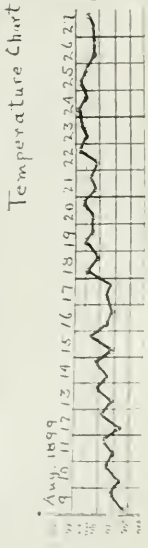
YEAR	1898									1899								
MONTH	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10
EXCITED		1				X				X	X	X	1	X		X	X	X	5
RESTLESS	X	X	±			X		X			X			X	X	X	X	X	X
NOISY	X	X	±							X						3			
IRRITABLE						1	X										3		
AGGRESSIVE					1	1				3	2					2		1	
ABUSIVE						1													
RESISTIVE									6	X	X	X	X	X	X		X	X	X
LAUGHS																	2		
DENUDATIVE						X		X	X	X	X		X		X	X			
MASTURBATES							X	X					X	X	X		X	X	1
UNTIDY		4				X	X	X	X	X	X	X	X	X	X	X	±	X	X
SLEEP POOR	±	X	2	±	±		4			±	±	±		±		±			X
APPETITE POOR	±			±						±									X
ILL																			X



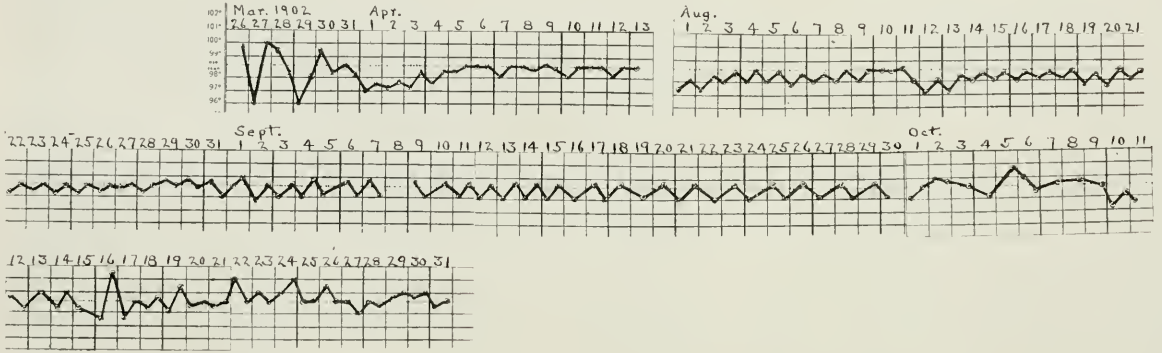
Case VII-41

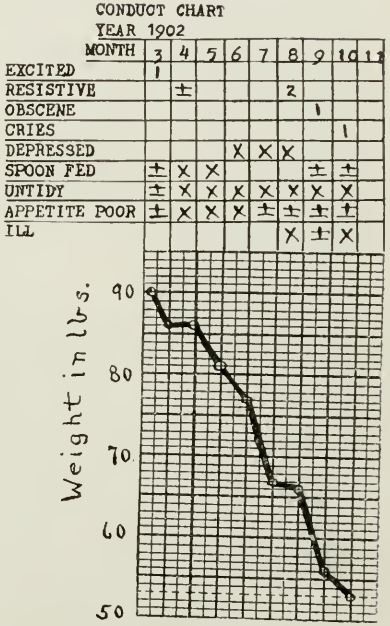
MENTAL	PHYSICAL	SUMMARY
Two or three years ago had nervous prostration.	Paternal aunt insane, father a suicide, brother peculiar. Menses at eleven, regular. At 14 came every 2 to 3 weeks and lasted 4 to 5 days. Appetite poor. Married at 19, because pregnant.	Active onset at 24 in a person somewhat handicapped with heredity at the start. Condition progresses over a period of three years or less, with insight at first but lost later. Obscure physical signs persist, almost from the start but definite signs appear only in the last month of life.
1898, November—Had delusions of poisoning against nurse at last confinement. Suspicious of doctor, husband, and mother drugging medicine. Auditory hallucinations.	1898, November—Headaches.	
1899, January—"Husband unfaithful with patient's mother." Cries, excited, abusive, aggressive, then remorseful.	1899, January—Weak.	
Spring—Knows when spells are coming, "a cloud comes over her brain."		
July—Applies for divorce (has cause).		
August—Stays out late nights with baby. Memory poor, orientation good, insight partial, "worse since coming to hospital."		
September—"Hears four different kinds of noises in her head at once," negativistic.	September—On getting up is dizzy and head goes round and round. Lies down much, "weak and lifeless."	
October—Cries, "abused by everybody," "imagines she sees false objects," "has a whirling in her head," "hears voices," "queer feeling in her head affects her heart," "a heavy feeling in her stomach."	December—"Too weak to do anything."	
1900, May—"I imagine that I am living and again that I am not," "I can not explain it for my mind goes from me and I am not here."	1902, March—Never heard to cough, appetite poor.	
December—Violent, aggressive, appropriates belongings of others, resistive, tries to escape.	April—Hemorrhage from lungs. "cheesy particles," no bacilli. Cough, rales. Stupor. Exit.	
1901, August—Auditory hallucinations; carries head high and hair in a peculiar fashion.		





MENTAL	PHYSICAL	SUMMARY
Seclusive and religious. 1901, March—Constantly talking religion, irritable, wanders on street, refused food, untidy, drools, spits, mute for past six months. Injures self by bumping head. 1902, March—Holds positions, fingers flexed in hands, negativistic, tube fed, inactive, irresponsive. April—Motionless, resistive. June—When touched jerks sharply away. October—Profane, talks after long period of muteness, resistance in eyelids later. Stereotyped expressions. Thinks some one is under her bed. Speaks of dying. Mute at times, resistive, negativistic, disoriented, confused. Says she spits up brown stuff that looks like chicken but it goes down again. "I used to sleep and never wake up, of course I didn't die." Memory poor.	Brother insane (?). 1901, March—Insomnia, loss of weight. 1902, March—Offensive nasal and vaginal discharge. Edema of feet and upper lids. Reflexes exaggerated. Appetite poor. July—Bed for weakness. October—Limbs cold, temperature begins. No cough. Asks for brandy for diarrhea. November—Complains of being smothered. Exit.	Active mental and physical symptoms begin at 44. Both persist unabated till the end about a year later. Temperature said to begin two months before death. Autopsy—Cause of death: Pulmonary tuberculosis (protocol missing).





CASE XII-28

MENTAL	PHYSICAL	SUMMARY
1906, September—Stupor of 6 to 8 hours' duration. October—"Going to be cut," wishes he were dead. Can not get well, has no life, is all gone. Careless, unsociable. 1907, July—Mute few days, screamed, refused food, "everybody is eating too much," "people called him a freak." Says he has not been well and that the night before admission was a blank to him. Answers slowly and stupidly. Staring for three weeks, solitary. On admission was resistive, suicidal, noisy and mute.	1906, September — Violent headaches, anemia. 1907, July—Has lost weight past year. Insomnia last three weeks. Systolic murmur at apex, over precordia and in axilla. P.M. rise in temperature, weak, bowels move only with oil enemas. Exit.	Onset at 19 with stupor and active symptoms following. Death in about a year. Initial loss of weight which continues, with an afternoon rise in temperature noted in the last month of life. Autopsy—Beneath left 6th rib is a pocket of thick reddish pus. Right apex nodular. Pleura slightly adherent. Death from tuberculosis.

CONDUCT CHART

YEAR	1907
MONTH	7
EXCITED	X
RESTLESS	X
RESISTIVE	X
DEPRESSED	X
APPETITE POOR	X
ILL	X

CASE XIII-17

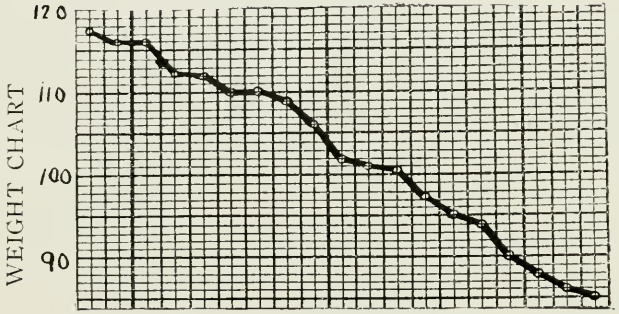
MENTAL	PHYSICAL	SUMMARY
1907, June—Thought everyone was doing wrong, fault-finding, cries. "A man in front of him in church put an electric bullet through him." December—Dull and sluggish mentally. Dull and subject to anger for past two years. Would not associate with other workmen, gave up jobs without cause. Threatened to shoot himself and his mother. 1908, March—Oriented. April—Untidy.	Often had malaria. 1906—Slight cough noticed. One slight hemorrhage. 1907, June-December—In a Consumptives' Home. Emaciated. December—Anemic, weak, dry, hard cough. 1908, February—Aches and pains, diarrhea, pains in stomach. Dyspnea. March—Decubiti. Slight tendency to clonus in both ankles. Harsh, dry, crackling rales. Dullness at apex. April—Weak, hemoptysis. May 1—Death.	Physical signs became evident before the mental trouble. Course complete in about a year. Autopsy—Shows 75 c.c. of straw-colored fluid in peritoneal cavity. Mesenteric glands enlarged. Lungs adherent throughout. Pus cavity opened in removing sternum, numerous pus pockets in each lung. Ulceration of lower ileum and beginning colon.

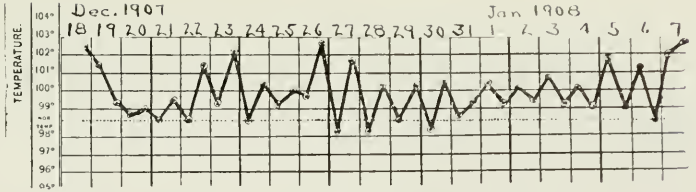
(See Chart, page 416.)

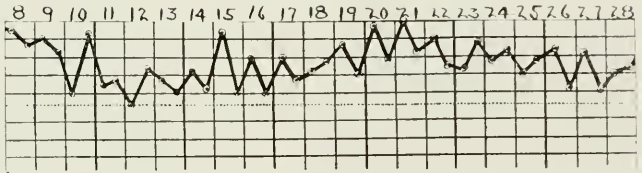
CONDUCT CHART

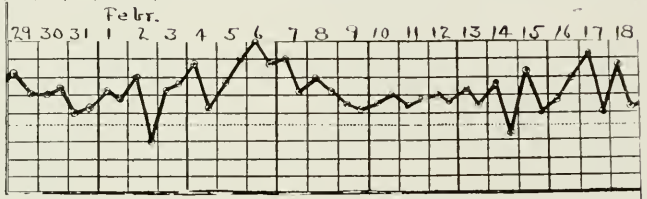
YEAR 1907 1908

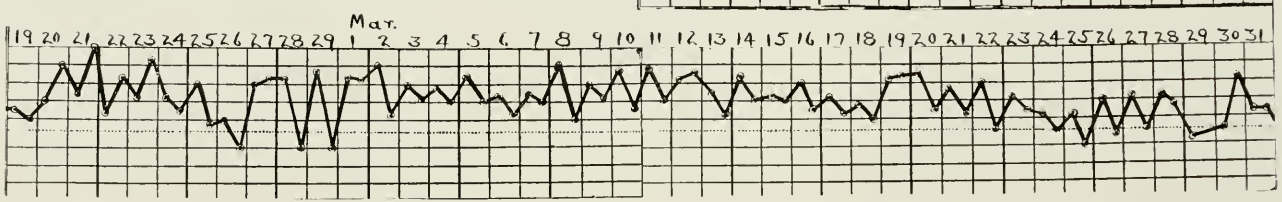
MONTH	12	1	2	3	4
UNTIDY					X
SLEEP POOR		X	±	X	X
APPETITE POOR	±	X	X	X	X
ILL	X	X	X	X	X

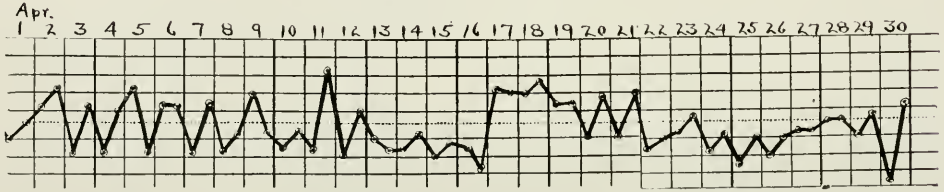








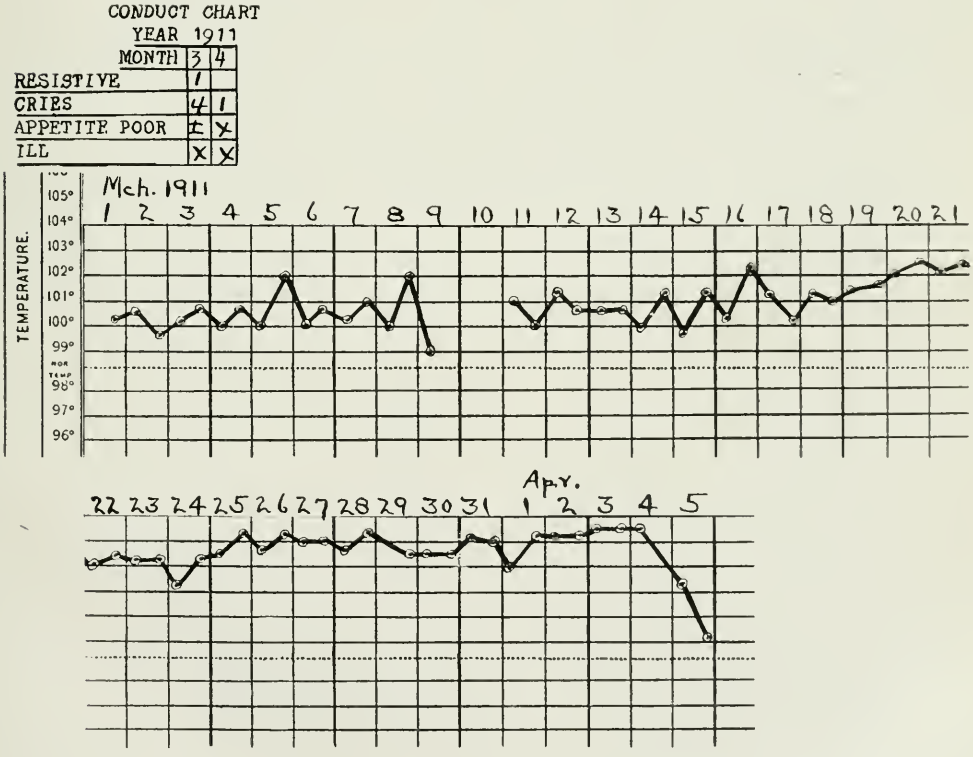




(See Table, page 415.)

CASE XVI-23

MENTAL	PHYSICAL	SUMMARY
1907 — Talked and acted strangely. Worse the past eight months. Talks to self, will not eat. 1911, March — Excited, depressed. "I see people around the walls, calling me." Fear affect. "They hit me on the head," "they fire bullets at me," "I am married" (patient is single). Dull, tendency to catalepsy, confused and sometimes apprehensive.	Has been in bed the past five months. Says she does not sleep. 1911, March—Weak, sallow, anemic. Lips and tongue dry. Signs at right apex. Sleeps poorly.	Gradual course of three years, ending with acute mental trouble and signs of tuberculosis. Autopsy — Right pleural cavity contains about 200 c.c. of slightly bloody fluid, left the same amount of puriform fluid. Old fibrous adhesions at apex. Anterior surface seat of thin, plastic, greenish-yellow exudate. Right lung nodular at apex. Left lung apex solid; section shows cavities. In upper and lower lobes are solid areas showing discrete and confluent, yellowish green areas, some with cavities.



CASE XVII-43

MENTAL	PHYSICAL	SUMMARY
1911, August—Onset gradual. Excited. A woman wanted to harm her. Could see her husband on the horizon. Talk rambling and incoherent, restless nights.	1911, August—Poor physical condition, lost weight, anemia, temperature, insomnia.	Physical condition parallels mental condition in a woman of 33. Exit in less than a year after onset.
1912, March—Noisy and restless nights. Fairly oriented for time, excited "because afraid of another patient." Partial grasp on surroundings, auditory hallucinations at home, no insight. "Has been sick for six months but not mentally."	1912, March—Feels tired. Below and to the left of the lower angle of the right scapula, dullness and bronchial breathing. Back aches and sore inside. Cough.	Autopsy—Decubiti. Old adhesions lower part of right lobe of liver and transverse colon. Right pleural cavity obliterated, left dense adhesions at apex. Scars at apex of each lung. Ileum seat of 13 ulcers which are shallow bright red, not particularly undermined, follow the circumference of the gut and show nodular elevations on the peritoneal surface.
May—Cries and is talkative.		
June—Resistive to attentions for past six weeks. Mute at times.	June—Diarrhea lately, loss of weight, temperature at night. Tubercle bacilli in feces. Exit.	

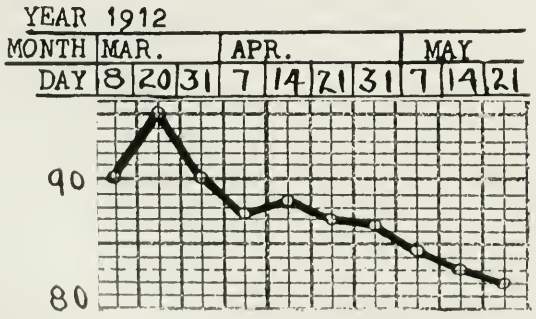
(See Chart, page 419.)

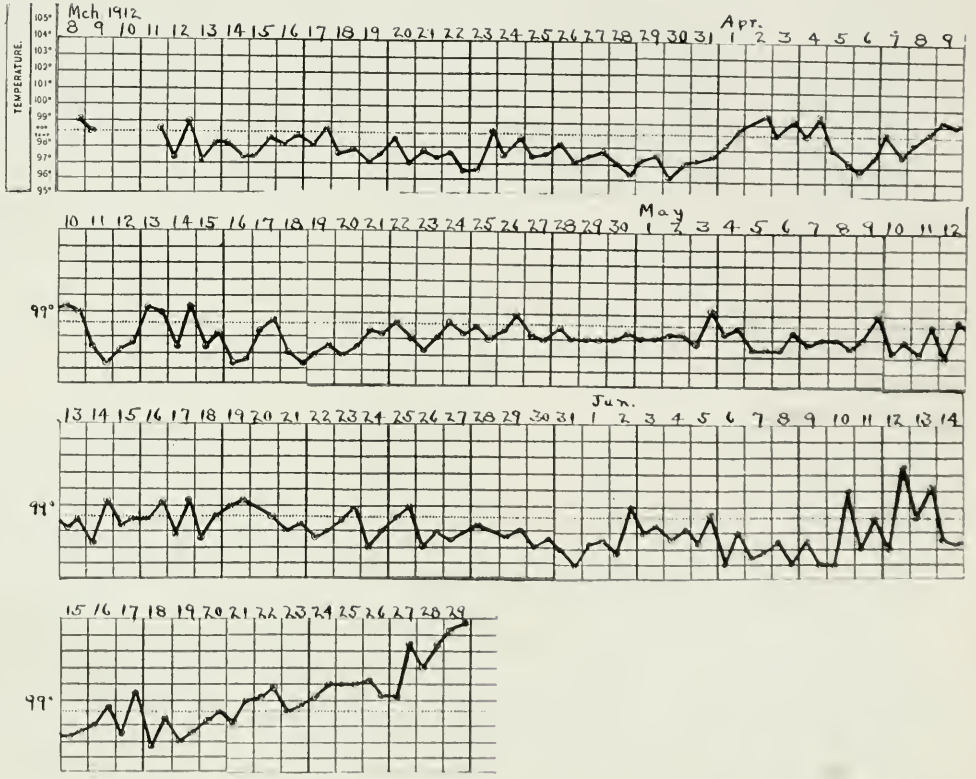
CONDUCT CHART

YEAR 1912

MONTH	3	4	5	6
EXCITED	1			
NOISY		2		4
RESTLESS	2		3	X
RESISTIVE			X	X
DEPRESSED			X	X
UNTIDY			X	X
APPETITE POOR	±	±	±	±
ILL	X	X	X	X

WEIGHT CHART





(See Table, page 418.)

CASE XIV-7

MENTAL

1912, December—Learning new job, got discouraged and gave up suddenly and went back to his old work. Saved his money in a handkerchief under his pillow and occasionally would loaf a few days and spend a little.

1913, February—Ideas of reference, careless in appearance, delusions of persecution, nervous, brooding, silent. Said sister-in-law doped his mother, threatened her. Makes mystic references. Rambling and incoherent at times.

April—Oriented, memory good, reticent, suspicious. Denies all previous actions and statements.

May—Attributes insomnia to poison but shows some uncertainty about it. Sensations of shivering and of difficulty in breathing, "fighting the world all alone." Later aggressive, violent, defiant, threatening, grasp fair, insight none. School knowledge retained. Food tampered with because of its effect upon him. Desires to study the Catholic religion.

1914, January — Hallucinations of sight, hearing and touch explained as the direct work of God. Stares, prays. Twitchings "caused by electricity." Tube fed.

February—Taking food is wrong so will not eat; expels feedings.

PHYSICAL

Father intemperate, apoplexy at 38, died at 41.

1912-'13—Insomnia.

1913, April—Tremor of fingers, knee jerks very active. Wassermann on blood negative.

May—Insomnia.

1914, January—Losing weight.

March—Exit.

SUMMARY

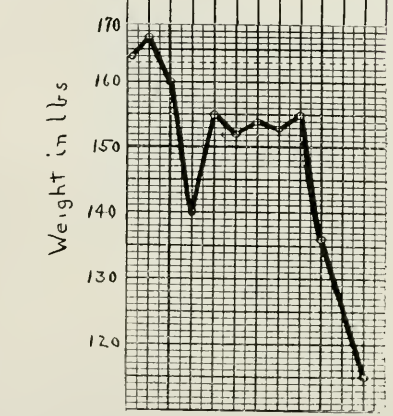
Duration of active symptoms little over one year. No physical signs discovered at any time.

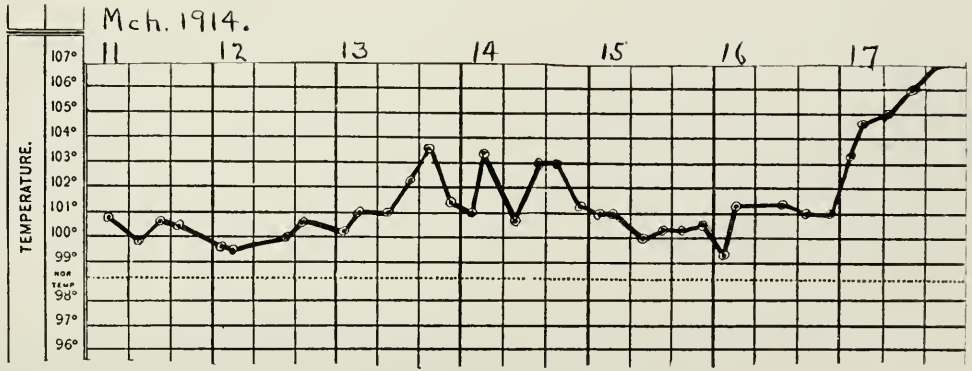
Autopsy—Right chest contains 30 c.c. cloudy fluid. Fibrinopurulent exudate between upper and middle lobes. Left lung is nodular. Abscess in upper lobe, surrounded by consolidation and many raised, white, coarsely granular areas surrounded by injection.

Duodenum the seat of gray, raised foci. Mesenteric lymph nodes slightly enlarged. Smear from lung positive for tuberculosis.

CONDUCT CHART

YEAR	1913									1914		
MONTH	4	5	6	7	8	9	10	11	12	1	2	3
EXCITED		2										
RESTLESS		X	X							X		X
NOISY		1										
RESISTIVE		2										X
AGRESSIVE		1										
IRRITABLE												6
PROFANE		1										6
DENUDATIVE												X
DEPRESSED		X	X	X	X	X	X	X	X	X	X	X
UNTIDY											X	
TUBE FED										±	X	X
ESCAPE TRIED		1										
WORKS		±	X	X	X	X	X	X	X	7		
APPETITE POOR		±				±	±	4	±	±		
ILL	2									±		X





Case 1916.25

MENTAL

Did well in school till fifth grade. A poor workman now getting worse. Unsociable, timid, stupid. Recently thought spies were drugging him. Restless, sighs a great deal.

1913, April—Speech disconnected, memory and grasp fair, education poor. Auditory hallucinations recently, references are made to his clothes, etc.; thinks he is drugged to make him drink. Irrelevant at times, insight none. Thought of suicide once. Speaks slowly and in low tones, admits difficulty in thinking.

December—Elopes but returns the next day and says the incident was due to "mental deliriousness."

1914, January—Indifferent, unsociable, memory and grasp good, sometimes evasive, confused, slow in replying, and somewhat irrelevant, has sexual ideas.

August—Oriented, confused, deluded, no insight.

1915, September—Mannerism of hanging head, replies monosyllabic.

1916, March—Restless.

PHYSICAL

Twelve children in family. One died in convulsions, two still-born (the last), one died suddenly at 15, one died of tuberculosis at 25, one insane and suicide, one brother drinks heavily.

Patient had nose-bleeds till 16, then none till last week. Headaches all life.

1913, April—Left back at angle of scapula an occasional rale, pupils react unusually promptly to light.

May—Wassermann on serum suggestive positive, later negative. Right pupil slightly larger than left. Blood pressure 155.

1914, February—Losing weight.

1915, May—Stops work in the Industrial Room, cough, tired, weak, tuberculosis right base, loss of weight, right lateral scoliosis.

June—Sputum negative.

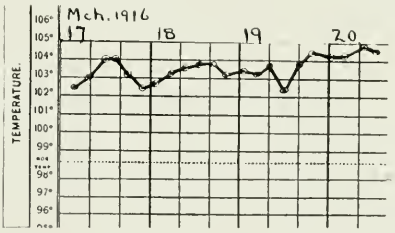
1916, March—Feverish. "Dementia precox sinking spells."

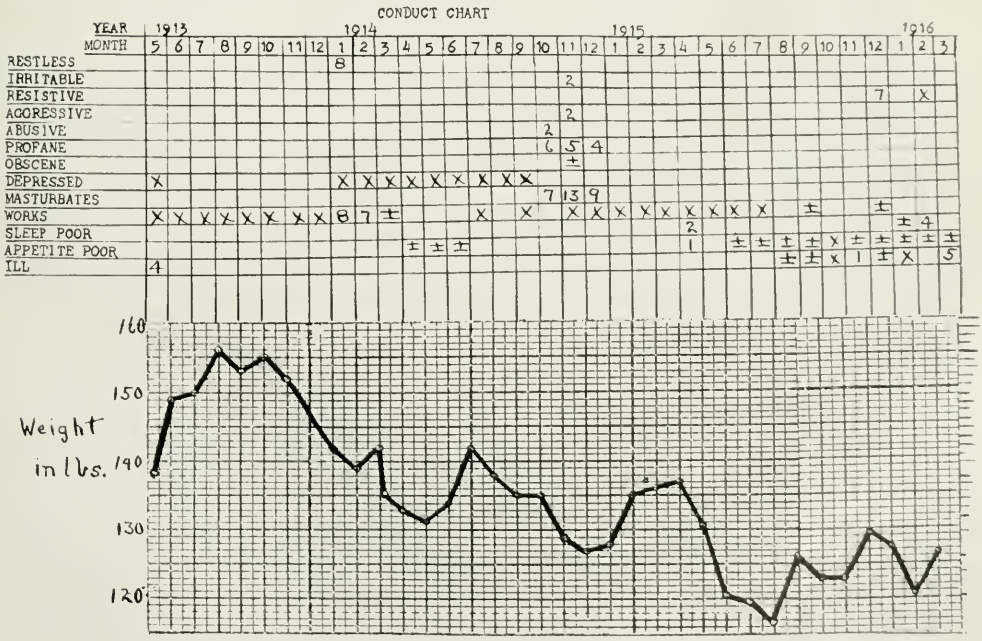
SUMMARY

Gradual onset at 24 leading to admission to the hospital two years later. Here patient remained in a confused and stupid state, though able to do a little work for a time, and died three years later. Physical signs made out almost a year before death.

Autopsy—Adhesions of intestines to ventral abdominal wall, both lobes of liver to diaphragm, spleen posteriorly, gall bladder to hepatic flexure and to small intestine, lungs anteriorly to pericardial sac, right lung at apex, posteriorly over upper lobe and externally over lower lobe, left lung at apex posteriorly and externally throughout. Consistency increased at both apices which are wrinkled and contracted. Rest of lungs nodular and granular. Two small scars left lung. Mesenteric glands much enlarged from behind pancreas down.

Transverse ulcers from middle of ileum down, more frequent at lower end. Small, round, yellow mass posterior to optic chiasm and another large yellow, granular mass in cerebellum, adherent to dura.





great groups from the mental side, independently of the physical picture. By "mental side," of course, one is to understand a combination of the purely mental as determined by mental tests and tests for orientation, memory, etc., and the conduct which is objective, to be sure, but which is an index of what is going on in the patient's mind, especially if considered from the viewpoint of behavioristic psychology. Such a differentiation into a toxic-infection group of catatonic form and a true dementia precox group (if such exist), would be of the utmost importance from the standpoint of prognosis and of rational treatment as against "empirical" treatment. The first would be amenable to treatment or would recover spontaneously but the second would be unfailingly fatal and its elimination would be a matter for preventive medicine, possibly of the eugenics type.

The question of remissions should also be of value in determining to which group any given case belongs. The case with remission should certainly be ascribed to true dementia precox with the greatest hesitation, if at all, if dementia precox is a constitutional dementing psychosis. The fact of remission should point to some other than a constitutional cause.

Turning to the physical side we note that a few cases showed signs of tuberculosis till shortly before death, if we consider only temperature and actual demonstration of the organism. If we review all the data, however, it is evident that tuberculosis might have been suspected in all these cases some time before the diagnosis was made. With present day methods, such as the roentgen rays, sero-diagnosis and other means by special culture media, which are notably few in the insane hospitals of the world and few enough in other hospitals, one might hope to suspect tuberculosis sooner, as we find that we can make the diagnosis earlier. With the continued loss of weight in these cases and the final cachexia one could scarcely make a mistake, but the diagnosis at that time is made too late. The anatomic findings in the lungs of all these cases would have given good roentgenograms long before they reached the stage discovered at autopsy.

Worthy of further attention are the headaches, epistaxis, weakness, the frequency of signs at the apex. Comparing these cases with the previous group we are struck by the frequency of positive findings in the sputum or the feces.

The severity of the lesions may be an index of the clinical course, not only of these cases, but of the cases of the previous paper which seemed, for the most part, to have recovered from the immediate effects of an infection and to have lived out a demented existence only to finally succumb to an exacerbation of the original trouble or to some other infection. An index to the long suspected course of tuberculosis and to the primary locus of infection is also apparent if the locus of lesions in this group is compared with the loci in the previous group. In that former series there were several cases of pulmonary and intestinal tuberculosis and an occasional one with tuberculosis elsewhere. In this present series there were four cases which showed intestinal lesions (XIII-17, XVII-43, 14-7, 1916.25). In addition to the intestine being affected, three of these cases showed enlarged mesenteric glands (XIII-17, 14-7, 1916.25). One case (III-24) showed enlarged glands without apparent involvement of the intestine. Four cases showed involvement of other organs (III-6, III-43, VII-41, 1916.25). This makes a percentage of 47 showing lesions in other loci than

the lung in this series and the percentage in the previous series was 46.1 or somewhat less, though the duration of the disease was longer in every instance in the first series. It is apparent that the pulmonary lesion is of prime importance in point of time and the intestinal lesion follows. Those with intestinal lesions seem to be in the more serious condition since they quickly die and even in the old cases, when intestinal lesions are found, they are fresh pointing to a fresh infection which was the terminal one.

Time appears to have little effect in the spread to the intestine if we are to draw any conclusions of this sort from the above percentages. Neither can we count on the temporal duration in the spread to other organs, though there seems to be some reason for taking time into account here since those cases of the second group (the present paper) which showed lesions in other parts than the lungs and intestines were those with longer duration, from two to four years.

Another interesting speculation is aroused when we consider that the mesenteric glands may be affected without apparent involvement of the intestine and that the abdominal organs may be involved without the apparent involvement of either the intestine or the mesenteric glands. With the assistance of our modern conceptions of infection, local and general resistance, and immunity, a large field for investigation should be opened in the field of psychiatry and tuberculosis which should rival, if not surpass that opened for the studies on paresis.

SUMMARY

Seventeen cases of dementia precox show a mental course and a physical picture so nearly parallel that one is taken to be the cause of the other.

This again opens the question as to the possibility of splitting the great dementia precox group into two main groups on the physical side: those of toxic-infectious nature, often tuberculous, and the true degenerative psychosis. This grouping has nothing to do with the mental groupings.

A wide field for investigation is outlined.

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THE RECENT EPIDEMIC OF INFLUENZA AND BRONCHOPNEUMONIA AT THE EASTON HOSPITAL, EASTON, PA.

Bacterial Findings

A Bacillus Resembling the Bacillus Pestis

By A. L. Kotz, M.D., Easton, Pa.

THE bacterial findings in material obtained from the lungs of 30 influenza and bronchopneumonia patients (mostly bronchopneumonia) either in the form of sputum, pleuritic fluid, lung tissue by aspiration or postmortem, were as follows: The influenza bacillus was found in 15; the pneumococcus (one type or another) in 27; a small diplococcus, forming short chains, in 14; streptococci of various types in 8; and a short thick bacillus in 24. The bacillus is the microorganism to which I wish to draw attention; the other bacteria mentioned have already been more or less thoroughly described by others.

The bacillus is short and thick, about 1.5×0.5 microns, with rounded ends. It occurs singly, in twos and short chains. It is very slightly motile, probably a little more than the ordinary Brownian movement. A capsule is seen in some specimens. Involution forms are common, and are oval, round or irregular. It stains with the ordinary aniline dyes. The ends of the bacillus stain more intensely than the middle. This polar staining is particularly well marked in specimens from the heart blood of inoculated mice stained with Giemsa's stain. It is Gram negative.

The bacillus grows at incubator and ordinary room temperature. On the primary plain agar culture it grows in tiny dew-drop colonies, not unlike the pneumococcus. In subculture it grows in moderately large grayish colonies which are slightly granular. In bouillon culture a moderate cloudiness is produced. If the bouillon is covered with oil after inoculation and allowed to stand undisturbed for a few days, fringe-like filaments develop from the under surface.

This bacillus is highly virulent for white mice. Injection of 0.1 c.c. of a 24-hour bouillon culture into the peritoneal cavity of a mouse kills the animal within three hours. The blood taken from the heart of the mouse contained the organism in large numbers. Mice inoculated subcutaneously with very small doses developed enlarged glands in which numerous bacilli were again found. A culture rubbed upon the shaven skin of a guinea pig produced an infection of the lymphatic glands. Pure cultures were again obtained from these glands.

From the fact that this bacillus is morphologically identical with the bacillus pestis, that it responds to the crucial test of Albrecht and Ghon, and that it is highly pathogenic for laboratory animals, we believe it to be, at least, closely related to the bacillus pestis. Again, from its frequent presence in this disease it would appear to have some significance.

ON THE DETECTION OF SMALL QUANTITIES OF TRICHLOROTERTIARY BUTYL ALCOHOL (CHLORETONE) IN THE FLUIDS AND TISSUES OF THE ANIMAL BODY

By T. B. Aldrich, Ph.D., Detroit, Mich.

CHLORETONE is one of the few organic drugs which (after its administration to an animal) persists as such in the fluids and tissues of the body for any length of time after being absorbed, while its slight solubility in water, its volatility with steam, its comparative stability, and its property of forming needle-like crystals make it possible, under certain conditions, to recognize it readily.

In a previous article (*Journal of Biological Chemistry*, 1918, xxxiv, 263) I have given a method for detecting small quantities of chloretone, either alone or when associated with substances that interfere to a certain extent with its recognition, and which lends itself admirably to the detection of chloretone in the fluids and tissues of the body where few if any disturbing factors are present.

In the stomach or intestinal content, in the urine, or in certain tissues that grind up to a fine pulp, it is only necessary to pass steam through them, but in certain tissues, for example, the blood or serum, it is necessary to subject them to a preliminary digestion with pepsin hydrochloric acid before distilling with steam, since coagulation takes place, and the small amount of chloretone usually present may be prevented from passing over with the steam.

The chloretone may be administered through the stomach in the form of tablets, crystals or capsules or intraperitoneally dissolved in water, oil, alcohol, etc. Both methods of administration may be employed, but regardless of method employed, the animal passes under the influence of the drug very quickly, the rapidity of action being determined by the method of administration, the condition of the dog, etc. The saturated aqueous solution in sufficient quantity works quite rapidly when given through the stomach, the rapidity being influenced by the quantity of food in the stomach, as well as other factors.

In the experiments carried out the dose usually exceeded considerably the M.L.D. of 0.25 gm. per kilo. The smallest dose given was 0.13 gm., the largest 2 gm. per kilo of body weight. Since the dogs were to be killed eventually, an excessive dose could be given without danger, as the animals would live a number of hours even after the administration of a large excess of the drug.

Although chloretone has been recognized in the fluids and tissues of the body only when comparatively large doses have been given, it is to be presumed that it is present and could be detected when small doses were employed, but then only in those organs that have an apparent affinity for the drug.

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Briefly, the general method of procedure consists in administering to the animal according to weight, a sufficient amount of the drug to produce complete anesthesia, waiting usually from two and a half to three and a half hours (in some cases longer), bleeding from the carotid artery (saving the defibrinated blood), perfusing with saline in order to wash out the remaining blood so far as practicable, removing the organs, reducing them when necessary to a fine pulp, digesting if necessary with pepsin HCl, subjecting to steam distillation, boiling distillate (using a return flow condenser) and examining the lower third of the cooled portion of the condenser for the typical needle-shaped crystals of chloretone.

Although it may not be necessary always to subject the pulp to steam distillation, or to a preliminary digestion with pepsin hydrochloric acid, it is advisable to do this in order to detect the smaller amounts of the drug. When needle-shaped crystals are noted near the crest of the condensing steam, or in the cooled condenser, becoming evident sometimes only after removal of the flame, the presence of chloretone is positive.

The amount of chloretone present has been estimated by comparative tests and is only an approximation.

The following fluids and tissues have been examined: blood, brain, bile, heart, intestine and contents, kidneys, liver, lungs, muscle, pancreas, spinal cord, spleen, stomach and contents, urine and vagus nerves.

One fact stands out very prominently: the nervous tissue, nearly without exception contains chloretone in varying amounts; while it is very frequently absent from the other tissues, and this would lead us to the supposition, which has been inferred but never proved relative to this hypnotic, that the nervous tissue has an affinity for it.

The greater part of the experimental work which follows was carried out a number of years ago when chloretone was first marketed as a hypnotic and anesthetic; but this work was not published at that time. Recently, owing to the wide use of the drug and the consequent new interest aroused in it, it was thought opportune to publish this older data, together with some recent experimental work.

EXPERIMENTAL

A. Recent Work

I. Weight of dog 13.5 kg. (Chloretone administered intraperitoneally.) Sixteen c.c. of a 40 per cent alcoholic solution, or 6.4 gm., given (0.47 gm. per kilo). Dosed 8:00 A.M. (11/8/17) going under in ½ hour. Bled at 8:30, 11/9/17, 80 c.c. of blood being obtained. Organs removed 10:15 A.M., nearly 26 hours after the administration of the drug.

The liquids (blood, stomach contents, and urine) were tested directly by placing in a suitable flask and passing steam through them. When about 100 c.c. of distillate had passed over, it was boiled over a free flame using a return flow condenser. The solid tissues were ground very fine by either passing through a grinder or rubbing up with sand in a mortar and distilled with steam, etc.

It will be noted in this experiment that the dog died 26 hours after the administration of the drug. Presumably most of it had been destroyed.

(1) Brain (wt. 46 gm.)	Positive (slight trace)
(2) Blood (80 c.c. defibrinated)	Negative
(3) Fibrin	"
(4) Liver	"
(5) Lungs	"
(6) Spleen	"
(7) Stomach contents	"
(8) Urine	Very slight trace (?)

II. Weight of dog 8 kg. Chloretone given per stomach; 3.2 gm. of chloretone given in capsules at 1:45 P.M.; at 4 P.M. 2 gm. given in 40 per cent alcohol, intraperitoneally. (0.65 gm. per kilo.)

At 4:10 P.M. dog bled from carotid artery (blood defibrinated). Organs removed two and a half hours after administration of drug.

Method of procedure same as in I.

(1) Brain (wt. 72 gm.)	Positive (½ mg.)
(2) Blood (defibrinated) (300 c.c.)	Negative
(3) Kidneys	Positive (¼ mg.)
(4) Liver	Negative
(5) Lungs	"
(6) Spleen (enlarged)	"
(7) Stomach contents	Positive (30 mg.)
(8) Urine	Negative

III. Weight of dog 7.5 kg. Chloretone given per stomach; 7.5 gm. given in capsules at 10:10 A.M. (1 gm. per kilo.)

Dog was completely under one hour later, and 3½ hours later was bled from the carotid artery, 250 c.c. of blood being taken. Warm saline solution was introduced into the femoral vein until 1200 c.c. had passed through and the wash collected from the carotid artery.

Organs removed 3½ hours after administration of the drug.

The stomach contents and the urine were distilled directly; the remaining organs were ground up and digested with pepsin HCl (250 c.c.) for two days. *Badly decomposed.*

The absence of any chloretone in all of the digested products is attributed to the fact that the flasks being insecurely corked allowed the chloretone to escape, and putrefaction to take place.

(1) Brain	74 gm.	Negative
(2) Blood	150 c.c.	"
(3) Heart	41 gm.	"
(4) Kidneys	21 gm.	"
(5) Liver	240 gm.	"
(6) Lungs	67 gm.	"
(7) Spleen	18 gm.	"
(8) Stomach Contents	50 c.c.	Positive
(9) Urine	60 c.c.	Negative

IV. Weight of dog 11.5 kg. Chloretone given per stomach; 3 gm. of chloretone in aqueous solution and suspension given at 10:20 A.M.

At 10:30 A.M. 5 gm. of chloretone in capsules given (0.7 gm. per kilo).

Dog gradually became completely anesthetized and 3 hours after the last dosing was bled and perfused with about two liters of saline solution. Dog died and autopsy showed that pressure of the perfusing fluid had been so great that it had caused a severe pulmonary hemorrhage.

Organs removed 3 hours after administration of drug. The urine and stomach contents distilled at once; the organs digested.

(1) Brain	Positive (50-100 mg.)
(2) Blood	Negative
(3) Heart	Very slight trace
(4) Kidneys	Positive (very slight trace)
(5) Liver	Negative (accident)
(6) Lungs	Positive (very slight trace)
(7) Spinal cord	Positive (5-10 mg.)
(8) Spleen	Very slight trace
(9) Stomach contents	Positive (300 mg.)
(10) Urine	Negative

V. Weight of dog 9½ kg. Chloretone administered per stomach; 5 gm. given in aqueous alcoholic suspension (250 c.c.) by means of a stomach tube. (0.35 gm. per kilo.)

Was bled from the carotid artery, just three hours after being dosed. The brain, spinal cord, and the vagi nerves were removed three hours after administration of the drug and ground up with sand and each digested with 250 c.c. of pepsin HCl for 16 hours in incubator at 37° C. Worked up in the usual way.

(1) Brain	Positive 20 mg.
(2) Nerves (vagi)	" trace
(3) Spinal cord	" 5 mg.

B. Older Work

VI. Weight of dog 7 kg. Chloretone given per stomach; 300 c.c. of aqueous chloretone solution 0.8 per cent or 2.4 gm. given (0.33 gm. per kilo). Went under in 1 hour. At the end of 2 hours, dog bled from the carotid artery (portion of blood saved) and an unsuccessful attempt made to wash out the residual blood from the body with saline solution.

Contents of stomach and intestine (upper part) were tested directly.

The organs were removed, washed to free them as much as practicable from blood, and then ground up and digested several days with pepsin hydrochloric acid, 500 c.c. of 0.4 per cent HCl and 2 gm. of pepsin (1:3000) being used in each case.

(1) Brain	30 mg. estimated
(2) Blood	40 " "
(3) Heart	5 " "
(4) Kidneys	Slight trace
(5) Liver	" "
(6) Lungs	None
(7) Muscle	Slight trace
(8) Spleen	" "
(9) Stomach contents	500 mg.
(10) Intestinal contents.	400 mg.

VII. Weight of rabbit ¾ kilo. Chloretone given per stomach; 1.5 gm. of chloretone given (2 gm. per kilo). Animal died soon after.

Brain removed and freed of blood as much as possible by washing in water.

Digested in pepsin HCl solution for 5 days. Treated in the usual way with steam, etc.

Brain	10 mg.

VIII. Weight of dog 6 kg. Administered per stomach; 100 c.c. of 0.8 per cent chloretone solution given, or 800 mg. (0.13 gm. per kilo). After 2 hours cannula was inserted into carotid artery and blood washed out as far as feasible from head and brain and the latter placed in refrigerator over night.

One-half of the brain was reduced to a pulp; distilled with steam, etc.

The other half was reduced to a pulp and digested with pepsin HCl (1 gm. pepsin 1:6000) for 4 days.

(1) Brain (direct)	Negative
(2) " digested	40-60 mg.

IX. Weight of dog 11 kg. Chloretone given per stomach; 150 c.c. of 0.8 per cent chloretone solution given: 1½ hours later 250 c.c. more given; finally ½ hour later 250 c.c., 6 gm. in all (0.55 per kilo).

(1) Brain	Crystals of chloretone 10 mg.
(2) Blood	Negative
(3) Heart	"
(4) Kidneys	"
(5) Lungs	"

X. Weight of dog 22½ kg. Given per stomach. Twenty 3-grain chloretone tablets and 500 c.c. of a 0.8 per cent solution of chloretone, 8 gm. in all (0.35 gm. per kilo).

In half an hour dog was completely under. Bled from carotid artery (200 c.c. blood obtained). Stomach and bladder removed.

(1) Blood	Positive
(2) Stomach contents	"
(3) Urine	Negative

XI. Weight of dog 6.4 kg. Chloretone administered per stomach; 320 c.c. of 0.8 per cent chloretone solution or 2.56 gm. total (0.4 gm. per kilo). Killed after 2 hours.

Removed organs after washing out with saline solution.

(1) Brain	10 mg.
(2) Blood	3-4 mg.
(3) Heart	2 mg.
(4) Intestinal wall	Negative
(5) Intestinal contents	0.5 mg.
(6) Kidneys	5 mg.
(7) Liver	10 mg.
(8) Lungs	1 mg.
(9) Pancreas	Negative
(10) Spleen	Negative
(11) Stomach	5 mg.
(12) Stomach contents	150 mg.
(13) Urine	Negative

XII. Weight of dog 9 kg. Chloretone administered per stomach; 350 c.c. of 0.8 per cent chloretone solution or 2.6 gm. (0.29 gm. per kilo) given. Killed after 1½ hours.

Brain removed and worked up in the usual manner. One-half distilled direct with steam; the other half distilled after digestion with pepsin HCl.

Blood and urine were also tested.

(1) Brain	50 mg. (100 mg. total)
(2) Brain (digested)	2.3 mg.
(3) Blood (digested)	5 mg.
(4) Urine tested for acetone	Negative

XIII. Weight of dog 9 kg. Administered per stomach. Had been used for digitalis work. Two hundred fifty c.c. of chloretone solution 0.8 per cent given, or 2 gm. (0.22 gm. per kilo). Killed after 3½ hours.

Brain divided into two portions and treated in the usual manner.

Heart and muscle also tested after digestion.

(1) Brain (digested)	2-3 mg. (4-6 mg. total)
(2) Brain (undigested)	Negative
(3) Heart (digested)	"
(4) Muscle (digested)	1 mg.

XIV. Wt. of dog 9 kg. Administered per stomach. Had been used for digitalis work.

Three hundred seventy-five c.c. of chloretone solution 0.8 per cent given; 250 c.c. given at first, did not go under, later 125 c.c. given (0.33 gm. per kilo). Went under then in a few minutes. In about 5 hours brain removed, ground fine and divided into two portions—one portion was digested in the usual manner. The other portion was treated at once.

(1) Brain (digested)	Positive 5 mg. (10 mg. total)
(2) Brain (undigested)	Negative

XV. Gave dog chloretone in aqueous solution 0.8 per cent 0.2 gm. per kilo of body weight (per stomach). Killed two hours after administration by bleeding. Blood washed out of circulatory system by saline solution before removal of organs. Organs washed also after removal. Blood was saved and tested for chloretone.

Organs ground fine and digested for 48 hours in 500 c.c. of water + 5 c.c. HCl (con.) and 2 gm. of pepsin U.S.P. at a temperature of 38° to 40° C. Each digestive mixture was distilled with steam, etc., in the usual way.

	WEIGHT GM.	CHLORETONE
(1) Brain	59	20-30 mg.
(2) Blood		Negative
(3) Bile		Mere trace
(4) Heart	85	10 mg.
(5) Intestinal walls		100 mg.
(6) Intestinal contents		30 mg.
(7) Kidneys	50	10 mg.
(8) Liver	234	Negative
(9) Lungs	120	100 mg.
(10) Pancreas		Negative
(11) Spleen	37	5 mg.
(12) Stomach		20 mg.
(13) Stomach contents	1900 c.c.	250 mg.
(14) Urine		Negative

XVI. Gave dog same amount as in XV, all conditions same.

(1) Brain	20-30 mg.
(2) Blood	Negative
(3) Bile (did not save)	
(4) Heart	10 mg.
(5) Intestinal wall	100 mg.
(6) Intestinal contents	10 mg.
(7) Kidneys	10 mg.
(8) Liver	Slight trace
(9) Lungs	Negative
(10) Pancreas	"
(11) Spleen	5 mg.
(12) Stomach	2 mg.
(13) Stomach contents	300 mg.
(14) Urine	Negative

XVII. Weight of dog 8.2 kg. Administered per stomach; continual dosage. Four tablets daily (3 grains) 2 in morning and 2 in afternoon or total of 60 grains = 4 gm. (0.50 gm. per kilo).

DATE	WEIGHT	PULSE	TEMP.	DOSE	REMARKS
6/29 A.M.	8200 gm.	96	103.2	6 gr.	
P.M.	8640 "	132	101.4	"	
6/30 A.M.	" "	144	101.4	"	
P.M.	" "	156	101.0	"	
7/1 A.M.	9090 "	168	101.2	"	
P.M.		168		"	
7/3 A.M.	8640 "	120	99.8	"	Weak, does not eat.
P.M.	7730 "	168	104.4	"	
7/5 A.M.	6000 "	136	100.0	"	Does not stand.
P.M.	6400 "	...	101.4	"	
7/6 A.M.		...	....		Found dead.

POSTMORTEM

Dog had been dead overnight and it was consequently difficult to distinguish anything abnormal during life from postmortem signs. Bladder greatly distended, containing 240 c.c. of urine. Acid in reaction. Sp. g. 1.030. Cloudiness, probably mucus or phosphates. The organs were ground up and treated in the usual way after digesting with pepsin HCl.

(1) Brain	1 mg.
(2) Blood	Negative
(3) Heart	Very slight trace
(4) Kidneys	Trace
(5) Liver	Spoiled, not worked up
(6) Lungs	" " " "
(7) Spinal cord	Negative
(8) Spleen	"
(9) Stomach contents	1 mg.
(10) Urine	Negative

XVIII. Weight of dog 5.5 kilo. Chloretone given per stomach; 300 c.c. chloretone solution 0.8 per cent. Anesthetized in 5 minutes. Was killed at the end of two hours by bleeding. Blood saved and organs removed from the body and freed from blood, so far as possible by washing first with saline and then with hydrant water. Digested with pepsin HCl for a few days.

(1) Brain	20-30 mg.
(2) Blood	20 mg.
(3) Heart	1 mg.
(4) Intestinal contents	Negative
(5) Kidneys	3-4 mg.
(6) Liver	Negative
(7) Lungs	1 mg.
(8) Spinal cord	?
(9) Spleen	?
(10) Stomach contents	30 mg.
(11) Urine	Negative

XIX. Weight of dog 11 kilo. Chloretone given per stomach; 600 c.c. of chloretone solution 0.8 per cent given, or 4.8 gm. (0.44 gm. per kilo). Anesthetized in 5 minutes. Remained under all day, sleeping quietly. Killed 6½ hours after drug was given. Bled from carotid artery and vascular system washed out with several gallons of normal saline solution. Dog was still breathing while perfusion was carried on. The organs were thus quite thoroughly washed free from blood. The following organs were removed, further washed with saline solution and tested for chloretone. Each organ was cut into small pieces and digested with pepsin HCl.

It was thought that washing out the organs removed the chloretone, still there was no chloretone found in blood before washing, or the drug may have been eliminated in 6½ hours. *The organs were incompletely digested.*

(1) Brain	Negative
(2) Blood	Negative
(3) Heart	Negative
(4) Kidneys	Negative
(5) Liver	Negative
(6) Lungs	Slight trace (?)
(7) Spinal cord	Negative
(8) Spleen	Negative
(9) Stomach contents.	Negative
(10) Urine	Negative

The presence or absence of chloretone in the summary table is indicated by the plus (+) or minus (−) sign. Where the space is blank the organ was not tested; and where a positive sign is followed by a number the latter indicates the estimated amount of chloretone in mg. while the letter (t) or a question mark (?) indicates a trace or a questionable trace. In the fifth column the letter *p* following "bled" shows that the animal was perfused; while in the fourth column "time elapsed" is the time intervening between the commencement of administration and the death of the animal. In 11 the drug was administered per stomach and intraperitoneally; in 1 intraperitoneally only; in all others per stomach.

An examination of the table shows that chloretone is uniformly present under varying conditions in the brain and in larger amounts and more constantly than in any other organ of the body, where the organ is taken in its entirety, there being all the way from a trace to 100 mg. or an average of about 24 to 25 mg.

When this measure is applied to the other organs and fluids we find the

Summary

DOGS	WT. IN KILO	DOSE PER KILO	TIME ELAPSED HOURS	MANNER OF DEATH	DIGESTED WITH PEPSIN	BRAIN MG.	BLOOD DEFIBRINATED MG.	FIBRIN MG.	GALL MG.	HEART MG.	INTESTINE (UPPER PART) MG.	INTESTINAL CONTENTS MG.
I	13.5	0.48	26.0	Died	No	+t	–	–				
II	8	0.65	2.5	Bled	"	0.5				–		
III	7.5	1.00	3.5	"	Yes					+t		
IV	11.5	0.70	3.0	" p	"	+100	–					
V	9.5	0.53	3.0	Bled	"	+20	–			+5		+400
VI	7.0	0.33	2.0	"	"	+30	+40					
VII	0.75	2.00	1.0		"	+10						
VIII	6.0	0.13	2.0	Bled	"	+60				–		
IX	11.0	0.54	2.0			+10	–					
X	22.5	0.35	0.5	"			+			+2	–	+0.5
XI	6.4	0.40	2.0	" p		+10	+4					
XII	9.0	0.31	1.5		Yes	+100	+5			–		
XIII	9.0	0.22	3.5		"	+3			–			
XIV	9.0	0.50	5.0		"	+10			+t	+10	+100	+30
XV		0.20	2.0	Bled p	"	+30				+10	+100	+10
XVI		0.20	2.0	" "	"	+30	–			+t		
XVII	8.2	0.50	84.0		"	+1	–			+1		–
XVIII	5.5	0.43	2.0	Bled p	"	+30	+20			–		
XIX	11.0	0.44	6.5	" "	"		–					
Average number of mg. found						24.25	4.9	t	0	2.5	66	90.1

brain contents is only exceeded by the intestine and intestinal and stomach contents. Here we would naturally expect to find an abundance of the drug (when given per stomach) depending on the amount administered, the length of time before the animal is killed, etc. Leaving these latter out of consideration, we find that the brain contains several times as much as the other organs. Perfusion does not apparently lower the chloretone content of the organs.

In most of the experiments the organs were digested with pepsin hydrochloric acid and this procedure *usually* increased the amount of chloretone obtained. The only exceptions are found in III and XIX where decomposition had taken place during digestion in the former, and where incomplete digestion was found in the latter. In one instance (XII), the half of the brain digested contained less chloretone than the half undigested.

It will be noted that in I only a trace of the drug was found in the brain and none in the other organs. Since the organs were removed 26 hours after dosing, it is to be presumed that the chloretone had been destroyed or eliminated.

In II a portion of the drug was given intraperitoneally dissolved in alcohol and its presence in only a small amount (0.5 mg.) in the brain after 2½ hours is explained by presuming that insufficient time for its absorption had been allowed.

In XVII 84 hours had elapsed which would account for the presence of only 1 mg. in the brain; while when we come to XIX, we find that the organs were very incompletely digested and that a rather long period of time (6½ hours) had elapsed.

In the spinal cord the drug was uniformly present except in XVII and XIX where the reason for its absence can be explained. In the vagi nerves the drug was found positively in V, the only one tested.

TABLE

KIDNEY MG.	LIVER MG.	LUNGS MG.	MUSCLE MG.	PANCREAS MG.	SPLEEN MG.	STOMACH MG.	STOMACH CONTENTS MG.	SPINAL CORD MG.	URINE MG.	VENEREE MG.	REMARKS
	–	–					–		+?		
+t							+30				
		–			–		+t				Flasks not
+t		+t			+t		+300	+10	–		corked tightly
								+5		t	decomposition
+t	+	–	+t		+t		+500				
		–									
							+		–		
+5	+10	+1				+5	+150		–		
									–		
			+1								
+10	–	+100			+5	+20	+250		–		
+10	+t	–			+5	+?	+300				
+t					–		+1	–			Fed for a
+4	–	+1			?	+	+30	+?	–		number of
–	–	–?			–	–	–	–	–		days.
2.6	1	9.2	0.5	0	0.9	5.4	130	3	0?	t	

It must be kept in mind also that idiosyncrasy plays a part in relation to this, as well as all other drugs, and may explain some of the variations in amount obtained in the tissues.

The experimental data above emphasizes the fact that the nervous tissue, especially the brain, seems to have a selective action for chloretone which would explain the hypnotic and anesthetic properties of the drug in a large measure. So far as I am familiar with the literature, this is one of the comparatively few instances in which the presence of drugs has been positively proven in the nervous tissues, although this has generally been assumed for a long time, and it is only possible in this case on account of the specific properties of chloretone.

The experimental data raises the question also of the selective action of hypnotics and anesthetics as well as other drugs, but places beyond dispute the selective action of this drug for the cells of nervous tissue, and makes probable the assumption of the selective action of other drugs for the tissues.

BENIGN TUMORS OF THE INTESTINE; WITH A REPORT OF NINE ADDITIONAL CASES*

By G. L. Rohdenburg, M.D.,† New York City

BENIGN tumors of the intestine are of infrequent occurrence, as is shown by Williams,[1] who in 15,481 cases of tumor found the intestine involved but 99 times, an incidence of one-half of one per cent. Of these tumors, 98 were carcinomata and one a sarcoma, no benign tumors being found. King[2], quoting the Mayo reports, states that but 8 cases of true solitary intestinal tumors occurred in the course of 44,654 laparotomies.

The most recent summary, that of King,[2] places the total number of microscopically confirmed cases on record as 124. King's summary is not complete since he has omitted reference to Stetten's[3] two cases of submucous lipoma, and to the latter author's summary of 149 cases of this type. A myoma recorded by Wood[4] is also not mentioned. In addition to these we can recall two cases of fibroma, one reported by Moschcowitz, and another reported by Elliot, both of which were confirmed microscopically; unfortunately, however, the exact references are not available. In addition to King's summary there are several other papers of interest, notably the first collection of cases by Heartaux,[5] and others of more recent date by Dewis,[6] James and Sappington,[7] Voeckler,[8] and one not quite so recent by Adami.[9]

Accepting King's summary as accurate for all practical purposes, we find the various tumor types distributed as follows: fibromata, 16; adenomata, 17; myomata, 45; lipomata, 29; angiomata, 3; teratomata, 2; fibromyomata, 3; neurofibromata, 3; fibroadenomata, 2. Forty-six of these tumors occurred in males, the age periods ranging between 17 and 75 years, while 61 occurred in females, the ages varying between 13 months and 83 years. The distribution in the intestinal tract was as follows: duodenum, 5; jejunum, 8; ileum, 24; ileocecal region, 3; appendix, 1; colon, 22; rectum, 36; vaguely located, as small intestine or intestine, 21. Two things are apparent from this summary; first, that these tumors are more common in the female; second, that they are most common in the rectum and colon. There is no apparent characteristic age incidence.

The clinical symptoms to which the benign growths give rise are of a most indefinite character. Not at all infrequently the growths are accidental finds at operation or autopsy. Occasionally they give rise to vague intestinal symptoms or to intestinal hemorrhage. The most frequent symptom is an intestinal obstruction due either to an actual blockade of the intestinal canal by the bulk of the tumor, or to an intussusception.

Analogous tumors occur in animals, Bullock having observed one such case at the Crocker Laboratory; I am indebted to him for permission to re-

*Of the cases reported in this paper, Cases 1 and 4 were observed in Lincoln Hospital, the remaining seven occurring at the Lenox Hill Hospital.

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port this instance in the present paper. The tumor was found at autopsy in a full grown rat and was noted as a localized thickening of the ileum measuring 3 mm. in diameter. Microscopic examination showed it to be a fibroma, which probably arose from the connective tissue of the submucosa (Fig. 1).

While the figures of the Mayo clinic give an indication of the infrequency of these tumor types, using as a standard all abdominal operations, a much more accurate estimate can be formed by considering their incidence in all intestinal tumors. The material available at the two institutions with which the writer is connected comprises 365 intestinal tumors, of which 345 were carcinomata, 3 sarcomata, 8 simple polyps, 3 fibromata, 2 lipomata, 1 myoma, 3 adenomata. Excluding the polypoid growths, there were 9 benign tumors, an incidence of 2.4 per cent. Of the two lipomata in the present series, one occurred in the appendix, and one in the ileum, both being of the submucous variety.

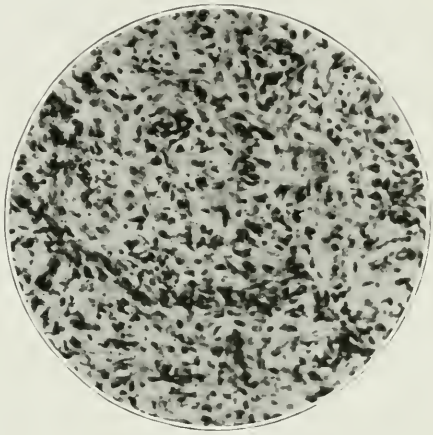

Fig. 1.—Fibroma of rat intestine.

Case 1.—Service of Dr. S. Erdman. The patient, a male, aged thirty-seven years, was brought into the hospital with a diagnosis of intestinal obstruction. At the laparotomy an intussusception, involving approximately 25 cm. of the ileum at about its middle, was found. The gut was resected and the patient made an uneventful recovery.

Upon opening the removed section of gut, the cause of the intussusception was found to be an encapsulated, soft, yellowish, ovoid tumor measuring 6 cm. in its longest diameter. This growth was situated beneath the mucosa. Histological examination showed a typical lipoma lying between the submucosa and muscularis layers of the intestinal wall. The mucous membrane over it was partially necrotic.

Case 2.—Service of Dr. F. Torek. The patient, a male, aged thirty-five years, was admitted to the hospital with the history and symptoms usual to an attack of appendicitis. He was successfully operated upon and made an uneventful recovery.

The appendix showed in the gross the common changes of an acute suppurative inflammation, and, upon being opened, showed directly beneath the mucosa 2 mm. from the tip, a circumscribed, yellow, ovoid mass, measuring 4×3 mm. in diameter. This mass upon microscopic examination proved to be a submucous lipoma in which there were marked acute inflammatory changes.

The one case of myoma in the present series occurred in the jejunum.

Case 3.—Service of Dr. Willy Meyer. A male, aged thirty-four years, was brought into the hospital suffering from a profound anemia subsequent to a violent intestinal hemorrhage. At operation the only discoverable cause for this hemorrhage was a tumor of the jejunum located approximately 30 cm. from the end of the duodenum. The portion of the intestine bearing the tumor was resected and the patient made an uneventful recovery.

The gross specimen consisted of a section of the small intestine 13 cm. in length. About one-third of the distance from the one end, there was an egg-shapped mass with its long axis at right angles to the long diameter of the intestine. The mass, which measured 5 × 3 cm., projected for about two thirds of its bulk beyond the normal intestinal wall and was covered by serosa. The consistency of the new growth was elastic, and section

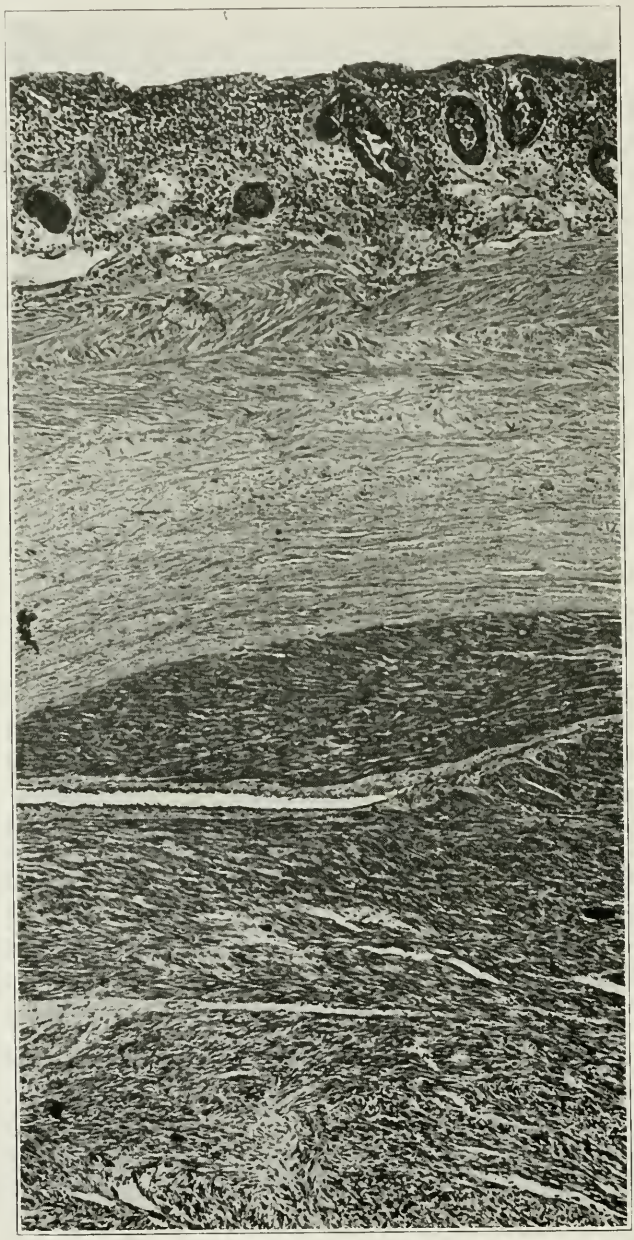

Fig. 2.—Myoma of jejunum.

through it showed it to be of uniform structure and red in color. Microscopic examination (see Fig. 2) showed the tumor to be encapsulated and covered by mucous membrane. The tumor itself was composed of interlacing bundles of smooth muscle fibers, which were moderately infiltrated with polymorphonuclear leucocytes. The tumor had arisen

from the inner layer of muscle, the outer layer though much thinned being still intact.

Of the three fibromata in the present series, one occurred in the rectum, the other two occurring in the ileum.

Case 4.—Service of Dr. F. Flynn. A female, aged twenty-five years, was admitted to the hospital complaining of intermittent attacks of intestinal hemorrhage, some of which were rather severe. Physical examination showed a pedunculated growth situated approximately 15 cm. from the anus.

The gross specimen consisted of an ovoid-shaped mass measuring 3 × 1 cm. in diameter. This mass was attached to a small fragment of the rectum by a short narrow pedicle. Microscopic examination showed the neoplasm to be composed of interlacing bundles of connective tissue fibrils with a scanty cellular content. Covering this connective tissue was a somewhat atrophic mucosa which presented areas of ulceration. The entire tumor, particularly just beneath the mucosa, was infiltrated with polymorphonuclear leucocytes.

Case 5.—Service of Dr. Willy Meyer. This case occurred in a male, aged fifty-two years, who was admitted to the hospital with the clinical symptoms of intestinal obstruction. Upon operation a large portion of the ileum was found to be involved in an intussusception. The intussusception was resected. The patient died of pneumonia five weeks after operation.

The gross specimen consisted of a section of the ileum measuring 70 cm. in length. At about the middle of the section of gut, the wall had been opened and there projected

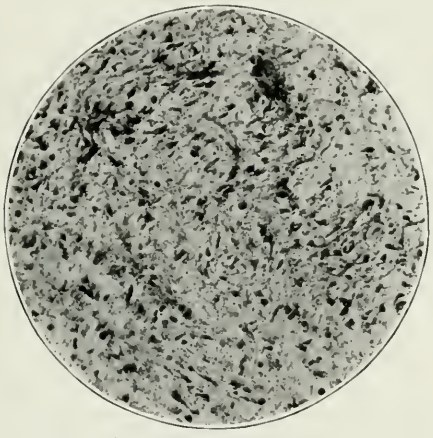

Fig. 3.—Fibroma of ileum.

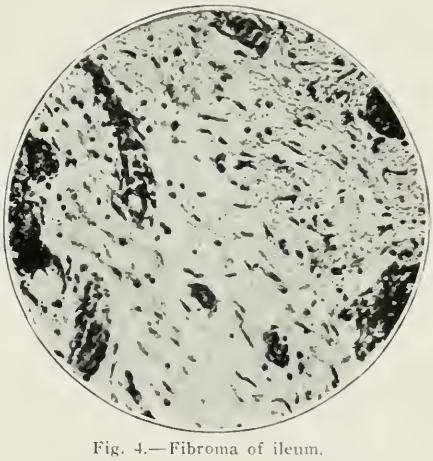

Fig. 4.—Fibroma of ileum.

a pedunculated firm mass, white in color and very resistant to section. This mass measured 6 × 4 cm. in diameter. Microscopic examination (see Fig. 3) of the growth showed it to consist of a very edematous connective tissue markedly infiltrated with polymorphonuclear leucocytes. Covering the growth was a very much necrosed membrane.

Case 6.—Service of Dr. Kammerer. This case occurred in a male aged forty years, who was admitted to the hospital with a diagnosis of intestinal obstruction. An intussusception of the lower portion of the ileum was found at operation. After resection of the intussusception, the patient made an uneventful recovery.

The gross specimen consisted of a segment of the small intestine and mesentery, which measured 70 cm. in length. The lumen of the distal, 15 cm. of which was composed of ileum had been incised longitudinally. In this portion of the lumen there was a large pear-shaped tumor approximately 10 × 6 cm. in diameter. The smaller end or pedicle of the tumor was attached to the wall of the gut 20 cm. from the ileocecal valve. The mucosa covering the tumor was ulcerated. Microscopic examination (see Fig. 4) showed the tumor to be a rather cellular fibroma composed of small spindle and stellate cells separated by a relatively large amount of fibrillar intercellular substance. These were arranged in irregular bundles and in the neighborhood of the blood vessels showed concentric lamellation. The surface of the growth was superficially infiltrated by polymorphonuclear leucocytes. In regions where the mucosa was still present, it rested directly upon the tumor substance which appeared to be directly continuous with the stroma of the mucosa.

Of the three adenomata reported in this paper, two were found in the rectum, and one in the ileum.

Case 7.—Service of Dr. Oastler. This case occurred in a female, aged forty years, who was admitted to the hospital complaining of rectal hemorrhages. Physical examination showed a growth in the upper portion of the rectum. This was removed and the patient made an uneventful recovery.

The gross specimen consisted of a soft cauliflower-like mass measuring 3×1 cm. in diameter. Microscopic examination (see Fig. 5) showed the growth to be composed of fairly typical appearing glandular acini for the most part straight and lined by epithelium which everywhere rested on a distinct basement membrane. Beneath the epithelial portion, the muscularis mucosa was intact and the submucosa showed no epithelial invasion.

Case 8.—Service of Dr. Torek. This case occurred in a male of thirty-seven years, who was admitted to the hospital complaining of persistent rectal hemorrhages. A pedunculated growth situated approximately 12 cm. from the anus was found at operation.

The gross specimen consisted of a soft villous mass measuring 5×4×1.5 cm. It was of purplish red color and irregularly divided into lobules. On the surface were numerous long finger-like projections running in all directions. On section the interior contained a narrow core of connective tissue from which the villi projected in all directions. Microscopic examination (see Fig. 6) showed the covering of the villi to consist of an irregular layer of mucous membrane composed of irregular glandular acini and epithelial papillæ. The epithelium covering the papillæ and lining the acini was of the high columnar type and in many places was laid down in several super-imposed layers. The glandular structures

Fig. 5.—Adenoma of rectum.

Fig. 6.—Adenoma of rectum.

were sharply limited to the surface, the connective tissue core in the interior being entirely free from invasion. In the core there was a rather marked chronic inflammatory round-cell infiltration.

Case 9.—Service of Dr. Stetten. This case occurred in a male, forty years of age, who was admitted to the hospital with a persistent abdominal sinus following appendectomy. At operation the usual appearance of a persistent sinus was found and in addition, a small rounded mass about the opening in the gut. This mass measured 2 cm. in its greatest diameter. Microscopic examination of this mass showed a chronically inflamed granulation tissue on the surface of which were found many irregular gland spaces lined by columnar epithelium which in some places was several layers thick. Some of these glandular spaces were dilated and filled with mucous. The deeper portions of the mass were free from epithelial invasion.

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LABORATORY METHODS

PICRAMIC ACID AS A STANDARD IN COLORIMETRIC DETERMINATION OF NITROGEN BY NESSLER'S METHOD*

By Grete Egerer, Ph.D., and Francis Ford, B.A., Minneapolis, Minn.

THE standard used in Nessler's method of nitrogen determination consists of ammonium sulphate and Nessler's reagent. This standard has the following disadvantages:

1. The ammonium sulphate solution becomes weaker with time, its concentration decreasing noticeably in as short a time as three weeks.

2. Nessler's reagent when prepared according to instructions given in most laboratory manuals on clinical work causes a precipitate in the solution. This, however, can be avoided by using Folin's modified reagent.[1] So far as our tests are concerned the solution never became cloudy when this reagent was applied.

3. The standard frequently begins to darken within eight minutes. A correction for the increase in color of the standard is impracticable as the change is irregular. Direct comparison of an old standard with a fresh one shows an increase in concentration sometimes up to 5 m. in half an hour, at other times showing only an increase of 1 m. in three hours. A standard can be used for only eight minutes with perfect safety. In clinical laboratories where a large number of tests are to be carried out in as short a time as possible, it is a great disadvantage to be compelled to change the standard after two readings.

Accordingly, for clinical work we suggest the blood sugar standard: picramic acid. (Dissolve 0.1 gm. of picramic acid and 0.2 gm. of anhydrous sodium carbonate in 30 c.c. of warm distilled water and dilute to 1 liter.)

This standard has excellent qualities:

1. The color is practically permanent. On comparing a solution of picramic acid made up two years ago with a freshly prepared solution, we found only a slight decrease in concentration, 0.06376 gm. instead of 0.0640 gm. Very likely this difference is due to an inavoidable inaccuracy in weighing. The lapse of time in this instance was greater than in any other test. In other instances the lapse of time was 1, 2, 3, 4, up to 6 months. The result was substantially the same.

2. All color comparisons in which Nessler's test can be used, can just as readily be made by picramic acid.

3. The main advantages are in the saving of time and absence of disturbing factors. During the influenza epidemic we made simultaneous analysis of

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a high number of bloods. We recognized the great value of the new standard. Our comparisons were made in a Hellige colorimeter. We do not, however, recommend the use of picramic acid as a standard for comparison in the Duboscq colorimeter, because, owing to the greater delicacy of that instrument the range of color tones is much limited. Nevertheless, the colors can be easily matched with a sufficient degree of accuracy in the Hellige colorimeter.

TABLE I

$(NH_4)_2 SO_4$-NESSLER'S AGAINST PICRAMIC ACID

Soln.	1		2		3		4		5		6		7	
	8.5	8.0	15.0	14.5	23.0	23.0	33.0	32.5	40.0	41.5	53.5	52.5	64.0	63.0
	9.0	7.0	14.0	15.0	23.5	23.0	32.5	33.0	40.0	40.5	54.5	53.0	65.0	62.5
	9.0	8.0	15.0	15.5	24.5	23.0	33.5	33.0	41.5	41.5	55.0	53.0	65.5	64.0
	9.0	8.5	15.0	14.0	22.7	21.5	34.0	33.0	41.0	41.0	53.0	53.0	64.0	65.0
	9.0	8.2	14.0	14.5	22.8	22.0	33.5	33.0	42.0	40.5	52.0	53.0	64.0	64.0
	9.5	8.5	14.8	14.5	23.0	22.5	34.2	34.0	42.0	40.0	52.5	52.8	63.0	63.0
	10.0	10.0	15.0	14.0	23.0	22.5	34.0	32.0	42.0	42.0	53.0	52.0	63.1	63.5
	9.0	9.0	15.0	15.0	23.0	21.8	34.0	32.0	41.5	40.5	53.0	52.3	64.0	64.5
	10.0	9.0	14.5	14.0	22.5	22.8	32.5	32.8	42.0	42.0	54.0	54.0	64.5	64.5
Aver.	9.23	8.5	15.02	14.56	22.24	22.55	32.32	32.25	41.49	41.28	51.46	51.77	62.61	63.82
	10.0	8.0	14.0	16.0	23.0	22.0	33.0	30.0	42.0	41.0	54.0	51.5	64.0	65.0
	10.2	8.0	15.0	15.0	22.0	23.0	33.0	32.0	44.0	41.0	53.0	52.0	64.5	64.0
	10.0	8.0	15.2	15.5	22.0	21.0	33.0	31.8	43.0	41.0	52.5	52.0	66.0	66.0
	10.0	7.5	16.0	15.0	22.0	22.5	33.0	32.5	40.0	39.0	52.0	51.0	62.0	62.0
	8.5	9.0	15.0	15.0	23.0	22.0	32.0	33.0	40.0	39.0	53.0	51.0	62.0	62.0
	9.0	8.8	14.8	15.5	22.8	22.0	32.0	32.0	41.0	40.0	53.8	52.2	63.0	63.0
	10.0	8.8	16.0	16.0	23.0	23.0	32.0	31.5	42.0	40.0	50.0	51.0	62.0	65.0
	9.0	8.8	15.0	16.0	22.0	22.5	32.0	31.5	43.0	41.5	52.0	51.0	64.0	64.5
	9.0	9.0	16.0	16.0	22.0	23.0	35.0	31.5	43.0	41.5	52.0	53.0	63.8	64.0
Aver.	9.52	8.44	15.22	15.56	22.42	22.27	31.98	31.81	41.99	40.44	52.55	51.63	63.63	64.00
	10.0	8.0	15.0	15.0	22.0	23.0	32.0	30.0	40.5	43.0	52.0	51.0	64.0	62.0
	8.0	8.0	15.0	15.0	21.0	23.0	31.0	30.0	41.0	41.0	51.0	51.0	64.0	62.5
	10.0	8.0	15.8	16.0	22.0	23.0	32.5	29.5	42.0	41.5	50.0	51.0	63.0	63.0
	8.0	7.5	15.0	14.5	20.0	20.0	32.0	33.0	40.0	40.0	51.0	50.0	63.0	61.8
	9.0	8.0	15.8	14.5	20.5	20.0	33.0	32.0	40.5	40.5	51.0	50.0	63.0	62.5
	9.0	8.0	15.8	14.0	20.5	20.8	32.0	31.0	41.0	40.5	52.0	51.0	63.0	63.0
	10.0	7.5	15.0	14.0	22.0	20.0	30.5	30.0	41.0	42.0	51.0	52.0	61.0	62.0
	9.0	8.0	15.0	15.0	22.0	21.0	31.0	30.0	40.5	40.0	51.0	50.5	60.0	63.5
	9.0	8.0	14.8	15.0	21.0	21.8	32.0	30.0	40.0	40.5	52.0	51.0	60.8	61.5
Aver.	9.11	7.9	15.16	15.16	21.22	21.31	31.77	30.61	40.77	40.99	51.22	50.62	62.42	62.41
Aver. of all determ. made	9.14	8.42	14.83	15.35	22.42	21.85	32.32	31.48	41.49	40.81	51.16	51.20	62.61	62.95

Table I contains three series of readings made with ammonium sulphate solutions of various concentrations. A solution containing 0.7866 gm. in 1 liter was made up. Solution 1 contains 1 c.c. of this stock solution in 50 c.c. Solution 2 contains 2 c.c. in 50 c.c.; solution 3 contains 3 c.c., etc. Three c.c. of the diluted solutions were treated with 2 c.c. of Folin's modified reagent and read against the blood sugar standard.

TABLE II

AMMONIUM SULPHATE-NESSLER AGAINST NESSLER'S STANDARD

Sol. 1		2		3		4		5		6		7	
13.0	13.0	20.0	21.8	32.1	29.5	40.0	39.0	49.5	47.0	60.0	56.0	68.0	68.0
14.0	13.0	20.0	21.0	33.0	29.0	38.5	38.0	49.5	49.0	60.2	57.0	67.5	67.0
13.5	13.5	19.5	22.0	33.5	30.5	39.0	38.5	50.0	48.0	59.0	58.8	69.0	68.5
130.0	13.0	23.0	20.0	32.5	32.0	40.0	36.0	48.5	48.0	57.5	59.0	59.5	66.0
14.0	13.5	24.0	20.5	31.5	30.5	41.5	36.0	49.0	48.0	56.0	58.0	69.5	66.0
14.3	14.0	23.5	20.0	32.5	31.5	42.0	36.0	49.0	48.0	56.5	58.0	69.5	66.0
14.0	14.0	22.0	22.0	33.0	33.5	42.0	39.0	49.0	46.5	56.0	54.0	68.6	66.0
12.5	14.8	21.5	22.8	32.5	32.0	40.0	38.5	51.0	47.8	55.0	54.5	66.5	62.0
13.0	15.0	23.0	23.0	32.5	32.0	39.7	39.0	48.8	48.0	55.2	55.5	67.0	63.0
12.0	12.8	22.0	22.2	30.0	30.0	41.5	38.8	50.5	50.0	56.0	59.0	66.0	61.0
12.5	13.0	21.5	22.5	29.0	30.0	40.0	39.0	51.0	49.0	57.0	58.8	67.0	60.5
13.0	13.0	23.0	22.0	30.5	30.0	39.8	38.2	49.5	48.0	58.8	59.0	65.5	61.0
Average		21.91	21.65	31.12	30.87	40.33	37.66	49.49	48.15	55.3	57.27	66.93	64.58
Av. of all determinations		21.78		30.99		38.99		49.0		56.31		65.75	
Max. read		24.0	23.0	33.5	33.5	42.0	39.0	51.0	50.0	60.02	59.0	69.5	68.5
Min. read		19.5	20.0	29.0	29.0	39.0	36.0	48.8	46.5	55.0	54.0	65.5	60.5
Diff. expressed in mm.		4.5	3.0	4.5	4.5	3.0	3.0	2.2	3.5	5.02	5.0	4.0	8.5

Table II is intended to show that analogous variations of readings occur when Nessler's standard is used. The standard was used for but two determinations. The same solutions were employed as in Table I. The numbers in the last row show that the readings may vary to a considerable extent. The average error amounts to 4.03 mg. and 4.58 mg., respectively, as against 3.48 mg. and 3.21 mg., respectively, in Table I.

TABLE III

TABLE FOR ESTIMATION OF NITROGEN WITH MODIFIED HELLIGE COLORIMETER USING PICRAMIC ACID AS A STANDARD

COLORIMETER READING	MG. N IN 100 C.C. BLOOD	COLORIMETER READING	MG. N IN 100 C.C. BLOOD	COLORIMETER READING	MG. N IN 100 C.C. BLOOD
63	35.18	44	26.77	25	16.42
62	35.75	43	26.29	24	15.91
61	34.33	42	25.81	23	15.40
60	33.90	41	25.24	22	14.89
59	33.48	40	24.67	21	14.19
58	33.05	39	24.11	19	13.48
57	32.63	38	23.55	18	12.78
56	32.20	37	22.99	17	12.08
55	31.78	36	22.43	16	11.37
54	31.35	35	21.86	15	9.96
53	30.93	34	21.30	14	9.19
52	30.50	33	20.94	13	8.42
51	30.03	32	20.02	12	7.64
50	29.65	31	19.50	11	6.87
49	27.17	30	18.99	10	6.10
48	28.69	29	18.48	9	5.33
47	28.21	28	17.97	8	4.58
46	27.73	27	17.45	7	
45	27.25	26	16.94	6	

Table III was calculated from the average of a large number of determinations of ammonium sulphate solutions prepared from pure ammonium sulphate. Calibrated Ostwald pipettes and volumetric flasks were used throughout. The solutions were made up just before use. The temperature of the solutions was kept constant. The comparisons were made with the Hellige colorimeter.

Our findings for nitrogen expressed in mg. for 100 c.c. of blood obtained by comparison with Nessler's standard do not exactly coincide with those of Myers and Fine.[2]

Expressed in mg. N. in 100 c.c. of blood:					
2	3	4	5	6	7
12.4-10.01	17.50-15.01	21.75-20.02	27.0-25.22	31.09-30.02	35.61-35

The first figures of each concentration are taken from Myers and Fine. Invariably our findings are lower.

In general the findings with picramic acid as a standard are practically the same as with the ammonium sulphate standard, e. g., solution 4 is found to contain 20.02 mg. when read against Nessler's standard, 19.97 mg. (calculated for 100 c.c. of blood) when compared to picramic acid.

Picramic acid is easily prepared from picric acid by a modified method (Jour. Biol. Chem., 1918, xxxv, 565). The following process for purifying picric acid has been found satisfactory in practice: 100 gm. of Baker's chemically pure moist picric acid are heated in 750 c.c. of distilled water until completely dissolved. To the hot solution 24 gm. of anhydrous sodium carbonate (125 gm. crystalline) are added and the solution is filtered through a folded filter. To the hot filtrate about 5 gm. more of the carbonate are added. The mixture is allowed to cool, then filtered on a Buchner funnel, washed twice with water (10 c.c. each time) while still on the funnel. The precipitate is then decomposed with 250 c.c. of dilute sulphuric acid (diluted 1 to 10) in a porcelain dish, and the residue filtered off on a Buchner funnel, washed twice with water (10 c.c. each time). It is then twice recrystallized from alcohol, 60 to 80 c.c. being used the first time, about 40 c.c. the second time. The yield is about 70 per cent. The entire process takes about two hours.

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A PEROXIDASE REACTION WITH SODIUM NITROPRUSSIDE AND BENZIDINE IN BLOOD SMEARS AND TISSUES

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THE demonstration of a peroxidase reaction within certain white blood corpuscles has led to the view that the presence of this activity is a point of distinction of cells derived from the bone marrow, differentiating them from

the lymphocytic series which do not exhibit this property. The reaction is especially prominent about the cytoplasmic granulations of neutrophilic and eosinophilic polymorphonuclear leucocytes, but seems to be absent within the basophilic cells. This chemical activity has been of use to the pathologist in aiding him to distinguish certain cases of myelogenous leucemia from the lymphatic type, but its application to the study of many problems of hematology, tissue pathology and the biochemistry of oxidization has been limited due, no doubt, largely to the unsatisfactory methods which have been proposed for its demonstration.

Until the methods of Graham were described the study of the peroxidase reaction within cells of smear preparations and tissues was an uncertain and more complicated procedure. The first method proposed by him was an adaptation of the well-known peroxidase reagent alphanaphthol with a counterstain of pyronin, two chemicals which are now scarcely available; and especially for this reason he was led to undertake experiments with other peroxidase substrates, with the result that quite recently he has advocated the use of benzidine for this purpose, his method of application giving more satisfactory results than previous investigations had obtained with this reagent. The technic is simpler than that of the alphanaphthol process, though the brown color reaction is not very striking or clean cut.

The use of these two procedures emphasizes the importance of the test and the desirability of a method simple enough to be used routinely and at the same time yielding uniform and clear results. In certain experiments recently I have devised a method for demonstrating the peroxidase reaction within leucocytes of smear preparations and in sections, which I am convinced will meet these needs; and it involves a chemical test for this activity, which to my knowledge has not heretofore been described, depending upon a color reaction with sodium nitroprusside.

The reagents and counterstain are prepared in a single stock solution of the following composition:

Alcohol 95%	100 c.c.
Sodium nitroprusside	.05 gm.
Benzidine (C.P.) (Harmer)	.05 gm.
Basic Fuchsin	.05 gm.
Hydrogen peroxide	.5 c.c.

The sodium nitroprusside is dissolved in as little water as possible (1 or 2 c.c.) and added to the alcohol; the other ingredients are then included. This stock reagent after some weeks has shown no deterioration in activity, although a slight flocculent precipitate settles out in a few days.

TECHNIC FOR SMEAR PREPARATIONS

Fresh smears of blood or other cellular material are permitted to dry thoroughly on the slide. The reagent is dropped upon it in sufficient quantity to cover the smear which is then allowed to fix for one minute. An equal quantity of water is added. A reaction time of three minutes has been in my experience sufficient. The preparation is finally washed out with water and dried by blotting.

The neutrophilic granules of polymorphonuclear leucocytes are stained deeply blue and are sharply defined. Eosinophilic granules are dark blue about their periphery with a lighter center. Basophilic granules do not seem to react. Fairly numerous and sharply defined granules are stained in the so-called transitional cells, and also in certain mononuclear cells of doubtful classification which with the usual stains would probably be grouped with lymphocytes. Most mononuclear cells show no reaction. Nuclei are stained a clear red, cytoplasm and platelets pink, and red blood corpuscles a smooth buff color. Altogether there is a sharp and pleasant contrast.

TECHNIC FOR FROZEN SECTIONS

Thin sections from tissue preserved in formalin are fixed to clean slides by means of gelatin, a method which I think has not been described, but has been used by me for some time with entire satisfaction. A stock of 2 per cent gelatin is kept in a test tube and melted when needed. A thick coat of it is smeared over one-half the slide and the section floated upon it. The section is blotted and pressed between filter papers, then fixed to the slide with a few drops of 95 per cent alcohol, which immediately hardens the gelatin. The section is then immersed in water and is ready for staining.

It is covered with the stock peroxidase reagent diluted with an equal volume of water. The reaction may be observed under the microscope and usually within three to five minutes the colors are sufficiently deep. The excess of stain is washed off in water, the section dehydrated with acetone, cleared in xylol and mounted in balsam.

The intensity of the stain may be readily varied both in smears and sections by varying the dilution of the stock reagent and the reaction time. Material fixed in formaldehyde and preserved in 80 per cent alcohol for several months reacts as rapidly and strongly as that freshly prepared.

The blue coloring substance resulting from the reaction of sodium nitroprusside and benzidine within cells containing peroxidase is insoluble in the ordinary solvents and seems to be permanent. Although investigations as to its nature and the character of reaction which takes place are incomplete, the method of staining has proved so simple and satisfactory that I feel warranted in describing it at the present time. The technic of application of the method to blood smears will be found quite as simple as that now employed with Wright's stain, and the reagent is sufficiently stable; while the resulting stain gives a preparation from which differential blood counts can readily be made. With a sufficient number of observations, differential counts based upon the presence of this important biological property in certain white cells and its absence in others may prove of more practical worth than those founded upon the morphologic differences exhibited by methods now widely in use.

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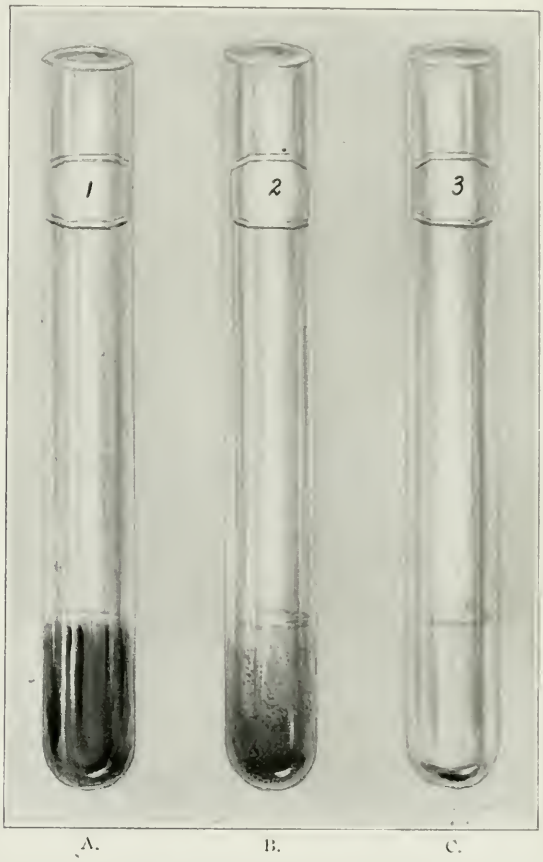
A LEAD PEROXIDE REACTION WITH SPINAL FLUID*

By Edward Steinfield, M.D., Philadelphia, Pa.

LEAD peroxide (PbO_2) is a dark reddish-brown powder, insoluble in water; specific gravity 8.903 to 9.190. A suspension of this compound in distilled water rapidly clears in a few moments, due to settling down of the particles to the bottom of the container. When a suspension is mixed with equal quantities of spinal fluid, the fine particles hold up considerably longer, but ultimately settle to the bottom of the test tube. If the fluid is normal, shaking up the sediment even after twenty-four hours or more, the original appearance



A.—Normal Fluid.
B.—Case of Tabes.
C.—Meningococcic Meningitis.

of uniform cloudiness is obtained. In pathologic fluids, such as from cases of the various types of meningitis, or syphilis of the central nervous system, a change takes place characterized mainly by adhesion or clumping with attendant precipitation so that on attempting to shake up the tube, large clumps of the metal are thrown about or, as in marked reactions, the entire mass sticks to the bottom of the test tube. This reaction has been applied in a comparative study of normal and pathologic spinal fluids with the result that the phenomenon of

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TEST NO.	NOGUCHI	GORDON'S TEST	CELLS				FEHLINGS	WASSERMANN	BACTERIA	LEAD PEROXIDE	DIAGNOSIS
			TOTAL PER CMM.	POLYS. PER CENT	S. L. PER CENT	L. M. PER CENT					
1	+	±	305	94	6	0	Reduced	Neg.	Meningococci	+++	Meningococcic meningitis
2	+	+	10	21	77	2	Reduced	Neg.	None	-	Fracture of skull
3	+	+	85	84	11	5	Not red.	Neg.	Meningococci	+++	Meningococcic meningitis
4	-	-	280	91	9	0	Not red.	Neg.	None found	++	Suspected epidemic meningitis
5	+	+	40	8	84	7	Not red.	Neg.	Tubercle Bac.	++	Tuberculous meningitis
6	+	+					Reduced	Neg.	Tubercle Bac.	++	Tuberculous meningitis
7	±	±	90	88	10	2	Not red.	Neg.	Pneumococci	+++	Pneumococcic meningitis
8	+	+	35	75	24	1	Reduced	Neg.	None	++	Meningitis (?)
9	+	+	850	91	9	0	Not red.	Neg.	Pneumococci	+++	Pneumococcic meningitis
10	+	+	12,500	95	4	1	Not red.	Neg.	Pneumococci	+++	Pneumococcic meningitis
11	+	+	1170	92	6	2	Not red.	Neg.	Meningococci	+++	Meningococcic meningitis
12	-	-	20	14	84	2	Reduced	Neg.	None	-	Concussion of brain (?) Meningitis(?)
13	+	+	750	90	9	1	Not red.	Neg.	Meningococci	+++	Meningococcic meningitis
14	+	+	480	88	10	2	Not red.	Neg.	Pneumococci	+++	Pneumococcic meningitis
15	+	+	8800	97	3	0	Not red.	Neg.	None	+++	Meningococcic (?) meningitis
16	+	+	860	96	4	0	Not red.	Neg.	Pneumococci	+++	Pneumococcic meningitis
17	-	-	18	16	83	1	Red.	Neg.	None	-	Tetanus
18	+	+	90	11	80	9	Red.	Pos.	None	+	Cerebrospinal syphilis
19	+	+					Red.	Pos.	None	+	Cerebrospinal syphilis
20	+	+	70	15	79	6	Red.	Pos.	None	+	Tabes
21	+	+	160	17	80	3	Red.	Pos.	None	++	Paresis
22	±	±	80	20	78	2	Red.	Pos.	None	+	Early tabes
23	+	+	11,600	96	4	0	Not red.	Neg.	Meningococci	++	Meningococcic meningitis
24	+	+	5400	11	80	9	Reduced	Neg.	Tubercle Bac.	++	Tuberculous meningitis
25	+	+	450	93	6	1	Not red.	Neg.	None	++	Meningococcic (?) meningitis
26	+	+					Red.	Pos.	None	++	Cerebrospinal syphilis
27	±	±	80	11	82	7	Red.	Neg.	Tubercle Bac.	++	Tuberculous meningitis
28	+	+					Not red.	Neg.	Meningococci	++	Meningococcic meningitis
29	+	+	10,400	97	3	0	Not red.	Neg.	None	+++	Meningococcic (?) meningitis
30	±	±	120	13	82	5	Red.	Pos.	None	++	Tabes
31	+	+	8200	96	4	0	Not red.	Neg.	Meningococci	++	Meningococcic meningitis
32	+	+	Blood in fluid				Red.	Neg.	None		Fracture of skull
33	+	±					Red.	Pos.	None	+	Cerebrospinal syphilis
34	+	+	1200	96	4	0	Not red.	Neg.	Meningococci	++	Meningococcic meningitis
35	+	+	820	92	7	1	Not red.	Neg.	Pneumococci	++	Pneumococcic meningitis

precipitation has been found to be only present in disease and uniformly absent in normal fluids. The degree of the reaction as measured by the time interval during which it appears and the completeness of precipitation have been of aid in indicating the nature of the pathologic process, as will be shown below.

The test is extremely simple and requires only a suspension of the lead peroxide, a few 5 or 10 c.c. pipettes and test tubes. The suspension is made up in the proportions of 1 gm. of the lead peroxide to 20 c.c. of distilled water and kept preferably in a wide bottle. The suspension is shaken up and 1 c.c. is placed in a test tube (12 × 1.5 cm.). To this is added 1 c.c. of spinal fluid and the whole shaken up for a few moments. The test tube is then allowed to stand in the open air and observed at the end of one-half to one hour and then the next day. The test can also be performed by having a number of test tubes already containing the 1 c.c. of lead and using them as desired. In this way they can be set up at leisure and large numbers of fluids quickly tested when necessary. To observe whether agglutination or precipitation of the lead has occurred, the tube containing the fluid to be tested and one containing a known normal fluid are placed in the same hand and shaken. In this way, the same amount of agitation is brought about in both tubes. The normal fluid will readily become uniformly opaque, the test fluid if abnormal will show some of the following reactions:

1. The particles of lead when shaken up will be coarse and uniform cloudiness of the tube will not occur. Settling takes place gradually.

2. The lead will be in the form of a few large clumps which settle quickly.

3. The lead will form in one clump which may stick to the bottom of the tube and resist shaking; by vigorous efforts it may be dislodged.

In addition, the time element is noted, since early and complete precipitation has been noted in cases of meningococcic and pneumococcic meningitis. The three types of reaction are conveniently designated in order, +, ++, +++. Except in complete precipitation it is well to check up the early observation by the 12 to 24 hour observation. The illustration gives the appearance of the reaction with a normal fluid, with that of a case of tabes, and one of a case of meningococcic meningitis.

The table gives the results with a number of pathologic fluids and a few from cases where meningitis was suspected, with the accompanying confirmatory data. The cell count has been omitted in those examined some time after the tap since it could not be made accurately at this time. About an equal number of normal fluids gave entirely negative results. I am indebted to Dr. Randle C. Rosenberger for a large number of fluids from the Philadelphia General Hospital upon which I made confirmatory observations.

CONCLUSIONS

1. A suspension of lead peroxide is not affected by normal spinal fluids.

2. Varying amounts of precipitation and agglutination occur regularly with abnormal fluids.

3. Early and complete precipitation is observed in the acute types of meningitis.

NEW METHODS FOR PRESERVING SOY-BEAN UREASE*

By G. M. Robinson, M.D., and C. J. Oppenheim, Ph.B., Chicago, Ill.

THE use of soy-bean extracts for the clinical determination of urea is now regarded as a standard laboratory method for rapid and accurate estimations of this substance in the urine and blood.[1] Many methods have been devised for preserving the active enzyme in the dry and wet states; but the former have, in general been unduly complicated, making it necessary to have recourse to clinical laboratories, while the latter have suffered for need of effective preservatives. Hence the clinician still finds it practical to adhere to the Doremus tube with its rather great percentage of error.

At the present time the most popular preservatives for the enzyme in the wet state are those of the toluol series. Toluol makes it possible to preserve the enzyme for about a week, if kept in the ice chest. This, however, necessitates the making of fresh extract at frequent intervals.

Tests have been made in this laboratory on the activity of enzyme extracts made according to the Marshall method[1] and preserved with various preservatives. Those employed were toluol, thymol, eucalyptol, benzol, chlorebutanol, glycerol, chloroform, phenol, ethyl alcohol, trikresol, and camphor. In each case .25 per cent of the preservative was used. The solutions were not placed in the ice chest, but allowed to remain at room temperature and tested at three and four day intervals. The following results were obtained:

Preservative	Number of days before extract failed to convert urea completely incubated at 35° C. for 2 hours or overnight at room temperature.
Phenol	7 days
Ethyl Alcohol	7 days
Trikresol	7 days
Benzol	10 days
Control (no preservative)	10 days
Chloroform	10 days
Toluol	13 days
Glycerol	17 days
Chlorebutanol	17 days
Thymol	17 days
Eucalyptol	20 days
Camphor	? (45 days; still active)

In each case, 2 c.c. of the enzyme converted a weighed quantity of urea (40 mgms.)

From the above tabulations, it may be seen that the preservatives most commonly used keep the enzyme slightly better than ordinarily thought; and without the usual precaution of keeping the preparation in the ice chest. It also demonstrates that neutral gum camphor is much more efficient as a preservative for soy-bean urease than toluol or the other common preservatives.

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We are able to say that camphor in .25 per cent suspension keeps the activity of the enzyme intact for at least 45 days.

In the hope of securing a permanent wet preparation of the enzyme, glycerol extractions were made with varying quantities of the powdered soy bean. It was found that the following method secured a preparation which answers all purposes and is, to the best of our knowledge, a permanent preparation.

TECHNIC

Twenty grams of powdered soy bean and 100 c.c. of pure glycerol are triturated in a large mortar to complete admixture. This mixture is then transferred to a percolator having a narrow lumen (the ordinary pharmaceutical percolator serves the purpose); and percolated through a layer of glass-wool of approximately one inch thickness for a period of not less than 48 hours. The resultant percolate is of a dark yellow color with a distinctly greenish tinge; and is ready to use after titration for innate alkalinity, *i. e.*, the amount of decinormal HCl required to neutralize one c.c. of the extract. (This need only be done once for the preparation.) This innate alkalinity we have found to be about equivalent to 2 c.c. of the decinormal acid, using methyl orange as an indicator.

One c.c. of the above glycerin extract suffices for ordinary clinical determinations where 5 c.c. of the urine are used. We can see no reason for the addition of acid as usually done in aqueous preparations, since it does not aid in the extraction; nor does it eliminate the necessity for determining the innate alkalinity of the extract. Glycerinized extracts are apparently more active than aqueous extracts of the enzyme, converting more rapidly especially when incubated at 35°C.

It is probable that the above method is equally applicable to extractions of the sword bean and jack bean, which according to Annett[2] and to Mateer and Marshall[3] are decidedly greater than the soy bean in their urease content. These would apparently produce glycerinized extracts of exceedingly high enzyme concentration. The matter is under investigation at present in this laboratory.

SUMMARY

1. The use of .25 per cent neutral gum camphor materially prolongs the period of activity of the enzyme in aqueous preparations of soy-bean urease, without complicating the technic for clinical determinations.

2. Glycerinized extracts of the enzyme afford an active and stable wet preparation which lend themselves readily to clinical procedure.

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A TYPE OF STETHOSCOPE RECEIVING BOWL FOR USE IN THE TEACHING OF MEDICAL STUDENTS*

By John A. Higgins, Chicago, Ill.

THE first practical knowledge that a medical student receives pertaining to the value of the stethoscope in medicine is generally given in the physiologic laboratories. When the period for instructions on the taking of blood pressure in the human begins, at least two known methods of procedure are mentioned. One is that which involves a sphygmomanometer, usually of a Tycos pattern, and a stethoscope, and is generally termed as the sound method. Another method of procedure, which involves a sphygmomanometer of an Erlanger pattern, including a recording tambour and revolving drum, is generally termed as the graphic method.

Where the latter, or graphic, method of procedure is employed in recording blood pressure, it is customary to record the findings on a glazed suface of a smoked drum paper previously gummed on the revolving drum. The blood pressure findings, or graphic tracing, is then interpreted to the students. Following these instructions the students should be able without much difficulty, to make further blood pressure tracings and interpret them.

In the sound method of recording blood pressure we must look upon matters from a different angle. Since an example can not be shown on the appearance of a sound, we must instruct students as best we can regarding what sounds to keep in mind while listening through the stethoscope. The types of stethoscopes ordinarily purchased on the market, no doubt, answer their purpose in the hands of trained medical practitioners. Among the beginning medical students, however, instructors have been compelled to rely upon the student's own decision as to whether or not they actually hear the arterial sounds and whether or not they hear them from the most advantageous areas. Feeling that much gain may be had by having an instructor himself continually listening in on the arterial sounds and also having a number of students listening at the one time, I have designed a new type of stethoscope receiving bowl as shown in Fig. 1. The head pieces that accompany this new type of stethoscope bowl are not changed over the older types but the possibility of four or even more listening from the same receiving bowl is assured.

The stethoscope receiving bowl is constructed by turning down on a lathe from a solid piece of metal, preferably aluminum, a piece similar in construction to piece *A* illustrated in Fig. 2. This piece of metal measures 7/8 of an inch in diameter on the top surface and 1 inch in diameter on the lower surface. A hole measuring 1/8 of an inch is drilled through the center. On the lower surface of this piece the drilled hole in the center should terminate into a conical-shaped opening measuring 3/8 inch deep by 13/16 inch as the greatest width. Also on the lower outside surface of this piece is threaded a hard rubber band *B*, using No. 32 or less threads to the inch. This hard rubber band sets out about 1/8 of an

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inch from the lower surface of the metal piece and thus prevents the metal itself from coming in contact with the skin or surfaces placed against. The metal piece at *C* measures $1\frac{3}{16}$ inches in diameter and comes flush with the diameter of the upper surface of the hard rubber band *B*. *D*, which is similar to a metal band permits the lower band *H* of the second section *E* to rest upon the upper

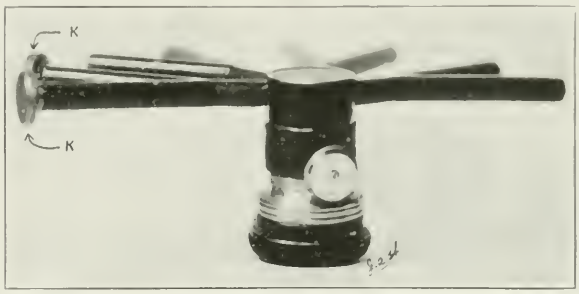

Fig. 1.—Showing a type of stethoscope receiving bowl and the possibility of four or even more listening from the same receiving bowl.

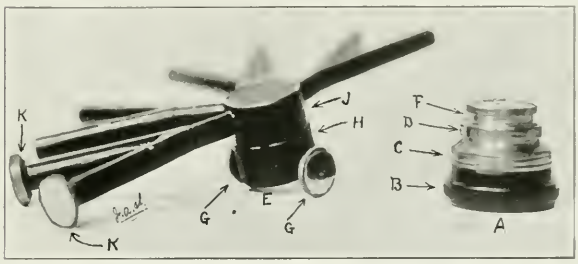

Fig. 2.—Showing the construction of a type of stethoscope receiving bowl.

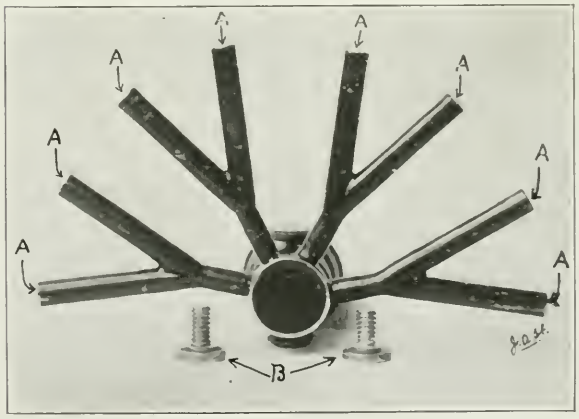

Fig. 3.—Showing top view of a type of stethoscope receiving bowl.

surface and as already shown in Fig. 1. At *F* is a grooved section $\frac{3}{32}$ inches wide which permits the $\frac{6}{32}$ threaded screws at *G* to lock sections *A* and *E* together. These screws at *G* need only be long enough to conveniently lock the two sections.

Section *E*, besides the set screws already described, consists of a lower band

of metal *H* 1/16 inch wall by ½ inch wide. This band rests on section *A* at *D*. A second metal band, *J*, with a closed top and measuring ¾ of an inch wide, is soldered into the metal band *H* just far enough so that the lower rims of the metal bands *H* and *J* will rest alternately on the upper surface at *D* and on the top surface of section *A*. On the outer side surface of metal band *J* are screwed in and then soldered firmly four Y-tubes of ¼ inch brass tube material. This does not mean, however, that only four individuals could listen from the one stethoscope receiving bowl at the one time, because in Fig. 3 is shown ample space for the addition of at least three more Y-tubes. Each Y-tube is connected in turn to the rubber tubes from the ordinary types of headpieces. As long as communication is cut off from the outside, the sounds heard from this type of a receiving bowl do not seem to diminish in clearness.

Where fewer individuals than projecting Y-tubes are to use a bowl of this type, the extra Y-tube or tubes are cut off from outside interference by threading the inside ends of the tubes at *A*, Fig. 3, and screwing in thumb screws *B*, Fig. 3. At *K* in Fig. 1 or 2 is shown a Y-tube thus cut off from outside communication.

While this type of bowl was primarily constructed for use in the physiologic laboratories, its use should not be limited to that field. Its use in the pharmacologic laboratories will permit a comparative study of blood pressure findings upon one another during and after the inhalation of such drugs as amyl nitrite, nitrous oxide, etc.

This type of bowl could also be used in a comparative study of reaction time. This is accomplished by students proceeding to take blood pressure readings from the brachial artery of a subject. Each student listening in on the stethoscope should also be equipped with a signal magnet, dry cell, simple key and a few lengths of copper wire for contact connections. Have each signal magnet arranged to record on a revolving smoked drum, using a rather rapid speed, and preferably a long paper drum. Each signal magnet, so recording, should be directly above one another. Now with the stethoscope bowl resting on the surface of the arm just below where the blood is shut off in the brachial artery, let each student with closed eyes listen for the blood to break through as the tension is removed from the artery. As soon as the first sound is heard let each student independently close the simple key at his command and thus record the first sound. Let some of the same group of students take an alcoholic drink or other mild stimulant and after the stimulant has had an opportunity to react upon the students repeat the experiment together with students under normal conditions, and note any changes in reaction of time. I might also suggest at this point the repeating of this experiment as a comparative study, between students who use tobacco and students who do not use tobacco or other such stimulant. An experiment somewhat along the same basis is already described by Jackson.*

*Jackson, D. E.: Experimental Pharmacology, 1917, St. Louis, C. V. Mosby Co., p. 143, Exper. xiii.

A TYPE OF CONTINUOUS THREADED ANEURYSM NEEDLE*

By John A. Higgins, Chicago, Ill.

THE aneurysm needle,[1] no doubt, seems to be an important instrument in the animal experimental laboratory. Some laboratory workers[2] prefer this instrument in separating muscle borders which thus gives them access to various underlying nerves and blood vessels. Other laboratory workers[3] prefer the threaded instrument in placing ligatures around nerves, blood vessels, or other body tissues. The instrument is also used in raising nerves or blood vessels from a wound while ligatures are placed underneath with the aid of forceps.[4]

In this latter case where forceps are used, in connection with the aneurysm needle in ligating nerves, blood vessels, etc., I am inclined to believe that the main reason the aneurysm needle is not used independently is because of the inconvenience and loss of time in threading or rethreading the present types. Occasions also arise where the loose ligature ends become entangled and thus accidentally separate the ligature from the eye of the needle.

Knowing therefore the value of the aneurysm needle in the experimental laboratory and endeavoring to increase its efficiency as a laboratory instrument I have accordingly designed a new type (Fig. 1).

The advantages offered in this needle are that the ligatures can be carried and kept on wound spools in the upper section of the handle (*A*, Fig. 1 or 2); the needle can be kept constantly threaded, provided ligatures are previously wound upon the spools or new spools of ligatures are inserted in place, using any grade of thread, or mercerized crochet thread, as some investigators may prefer. This will make it quite possible to place two ligatures around a nerve, blood vessel, or other body tissue in one operation. The ligatures passing through a sort of half round, open-faced tubing (*B*) eliminates, to a great extent, the danger of accidentally separating the ligatures from the eye of the aneurysm needle.

The aneurysm needle I shall describe can be made by taking a piece of hard or half hard brass metal measuring 5¾ inches long, ⅝ inch wide, and ⅛ inch thick. Drill a hole, using a No. 47 drill through the center of the ⅛-inch surface and 3/32 of an inch from one of the ends *C*. Cut and file away the metal in a similar fashion as shown at *D* and until the metal piece appears as an ordinary aneurysm needle having the widest flat surface at *E* measure 7/16 of an inch. On the back ⅛-inch surface, solder on a piece of ⅛-inch (outside diameter) brass tubing. File away a section of the ⅛-inch tube wall, as shown between the letters *F* in Fig. 2. This tube should now act as a shield for the ligatures and the filing away of a section of the outer wall should cause no inconvenience in threading.

A second piece of sheet brass metal measuring 4¾ inches long, ⅞ inch wide and 1/16 inch thick is bent into a U-shaped piece with the parallel pieces ⅝ inches apart. This piece is now trimmed down, rounding the corners, etc., and soldered to the end of the aneurysm needle at point *E*, Fig. 1. Two holes are now

*From the Department of Physiology, University of Illinois School of Medicine, Chicago, Ill.

drilled through this piece, using a No. 18 drill. Drill the first hole 3/8 of an inch, and the second hole 1-3/16 of an inch from the end at *G*, Fig. 1. Two round-headed screws of an 8/32 size, measuring 1-3/16 inches long, are taken and on the headed ends are soldered copper burrs, *H*, Fig. 2. These burrs simply reinforce the strength of the screw heads. On the threaded ends of the screws are used 8/32 size screw or lock nuts, *J*, Fig. 2. It is possible at this point, satisfactory, and economic to utilize screw or lock nuts taken from the binding posts of worn-out dry cells, this eliminates time and trouble in turning down the same size nuts on a lathe.

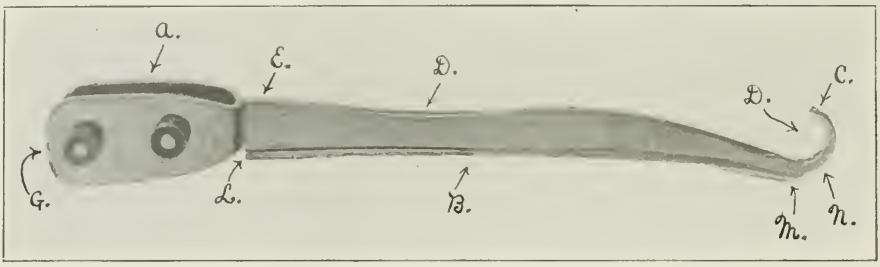

Fig. 1.—Showing a side view of the continuous threaded type of aneurysm needle.

The spools (*K*, Fig. 2) used in connection with this type of aneurysm needle were made from a piece of 3/4-inch hard rubber rod, which spools can be turned down on a lathe to fit into the spool holder. By regulating the lock nuts, *J*, Fig. 2, the friction on the sides of the spools can be increased or decreased at will. The spools in my case were not originally cut out for this particular aneurysm needle and thus necessitated copper burrs between the brass sides of the spool holder and the spools themselves. The spool holder will accommodate the wooden spools

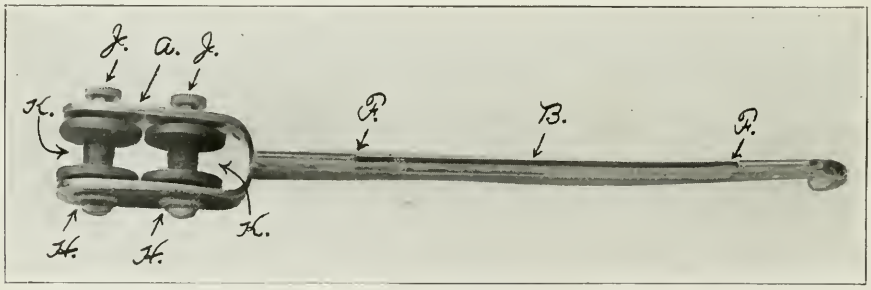

Fig. 2.—Showing a rear view of the continuous threaded type of aneurysm needle.

purchased on the market, which spools, as a rule, contain ten yards of silk thread. The advantage in this instance is that the spools purchased, already wound with thread, saves time in the rewinding of specially made spools. This size of aneurysm needle already described was originally aimed for mammalian work, smaller sizes for amphibian work can, of course, be made accordingly.

In threading the aneurysm needle, the ligatures after leaving the spools, pass through the tube opening at *L*, Fig. 1; past the tube opening at *M*; through the drilled hole at *N*, which hole was originally a part of hole *C*, and through the hole at *C*. Then to operate, after once threading the needle, raise the nerve,

blood vessels or other body tissue in the usual fashion as with the older types of aneurysm needles, procure a hold on the protruding end of the ligature or ligatures and remove the aneurysm needle in a careful manner. When you have secured the length of ligatures desired cut the threads about ¾ to 1 inch beyond the eye of the needle, which thus leaves the needle rethreaded for further ligations.

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EDITORIALS

Encephalitis Lethargica

UNDER the term encephalitis lethargica is included a series of cases observed in England, France, Italy, South America, and recently in the United States, in which the predominant symptoms are connected with the central nervous system. The distinctive features seem to be those of an acute general disease associated with a condition of languor, apathy, and drowsiness passing into lethargy; progressive muscular weakness passing into complete disablement; and a combination of various cranial nerve palsies, of which ptosis, squint, and nystagmus are characteristic signs. From the fact that the ocular muscles were so commonly involved, the disease has been called infectious ophthalmoplegia. Also, and because the disease has been supposed to be connected with food poisoning, it has been thought to be an expression of botulism. It has likewise been called epidemic stupor, acute polioencephalitis, bulbar paralysis, and Heine-Medin disease.

The suspicion that the disease is due to botulism has not been confirmed. In fact the investigations of the Local Government Board on Public Health

seem completely to eliminate this possibility, which had been so prominent. The investigators were unable to find the pathogenic organism and were unable to find evidence in serologic experiments of any suggestion of the presence of the bacillus of botulism. Histologic studies indicate an acute infection rather than an intoxication. Botulism is afebrile; this new disease is febrile.

Moreover, the studies of various men seem to show divergencies from the clinical and histologic picture of poliomyelitis that make it probable that the disease is a new one and not a mere modification of an old. And yet the lesions of the central nervous system resemble to a certain extent those found in general paralysis, syphilis, sleeping sickness, and acute poliomyelitis. Animal experiments also support the evidence that encephalitis lethargica is distinct from poliomyelitis, for inoculations into monkeys failed to produce paralyses. As a whole the findings to date are not satisfactory, but they point to the probability that encephalitis lethargica is a disease anatomically and clinically distinct from all others.

From the practical standpoint it has been suggested, says the Journal of the American Medical Association, that the appearance of this disease has been associated with a breakdown of immunity. Lowered resistance to a usually harmless saprophyte or a "conditional" parasite may be conceived to permit harm to arise from organisms ordinarily harbored with impunity. It is worth the mention that in the French epidemic there was a mortality of 50 per cent. In the series of cases reported by Porthier there was not a death. The reports from Camp Lee, Chicago and New York suggest the possibility that other cases may appear at other places in this country. So far all the cases in America have been in soldiers. This has not been true in England, though it has been the rule. Many of the cases have followed influenza.

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—*P. G. H.*

The Mechanism of Renal Excretion

THE physician who is seeking a knowledge of the function of the kidney in order to better interpret renal disease is quickly lost in the multitude of facts which rival hypotheses have gathered for their support. The modern text book of physiology is unable to give a review of the facts which are presented on literally thousands of pages of published researches, and the physician has never had a "close up" view of the subject. For this reason it is a great delight to take up the recent monograph on the Physiology of Renal Excretion, by A. R. Cushny of the London University.* For this book he has carefully sifted the enormous literature of the subject, and in a remarkably clear and entertaining style written

*Cushny, A. R.: Secretion of Urine, Longmans, Green & Co., London, 1917.

in a personal manner of the problem. Out of the tangled mass of facts presented by the literature he has evolved what he terms a "Modern Theory of Renal Excretion." He believes that this theory best explains the now known facts of renal function and that it will serve as a help in the understanding of renal disease.

The great number and the variety of substances which are found in the blood and the urine make it seemingly impossible that urine excretion depends on chemical combinations within the renal cells, and suggests a physicochemical mechanism to explain the phenomenon. The problem of how the kidney fabricates a highly concentrated solution of salts from a dilute solution of the same salts in the blood plasma is complicated by the fact that the ratios existing between the concentration of each urinary salt in the urine differs from that present in the blood. The urine is not a deproteinized blood plasma.

While it has not been possible to determine the nature of the forces which operate, it is possible to postulate that they function by one of two mechanisms. The one is that the urine is a filtrate of the blood which has passed through a portion of the renal epithelium into the tubules as a very dilute fluid, i.e., a deproteinized blood plasma and that the dilute fluid is concentrated by the absorption by physical chemical forces of fluid and salts by other cells of the kidney and replaced in the blood. The other mechanism would have it that the salts and the water are each actively excreted by the various cells of the renal epithelium. The first is known as the physical theory, and the second the vital theory of urine excretion. Both of these theories are inadequate to explain the phenomena which research has shown to occur in the kidney, but they have served to develop what Cushny terms "the modern theory of urinary excretion."

This modern theory accepts the general scheme of filtration and reabsorption of the physical theory, but pays due respect to the fact that the known physical forces are not adequate to explain the reabsorption which must take place to produce the concentration of salts found in the urine. It, therefore, supplements the physical theory by assuming a vital activity on the part of the epithelium of the tubules in reabsorbing fluids and salts from the dilute filtrate coming from probably the glomerulus and capsule. In short, Cushny's modern theory is as follows:

A large amount of blood plasma fluid is filtered through the glomerulus into Bowman's capsule, the filtering force being found in the blood pressure. This fluid has the same concentration of the salts to which the capsule is permeable as does the blood plasma. The blood leaving the glomerulus is, therefore, a somewhat concentrated solution of plasma colloids, and must have returned to it the proper amount of fluid and salts to make it an optimum fluid for the body cells. This is accomplished by the active absorption of a part of the glomerular filtrate by the cells of the tubules. The salts which are of no use to the body are not reabsorbed and, therefore, appear in highly concentrated form in the urine. These salts are termed "nonthreshold substances," and since their presence in the plasma is unnecessary, they continue to be excreted as long as they are present in the blood. The salts which are necessary are termed "threshold substances," and are reabsorbed until they are again present in the blood plasma in the optimum amount. For example, urea continues to be excreted as long as there is any present in the blood, while glucose is completely reabsorbed so long as its concentration remains under a more or less fixed level.

Although it is quite impossible to develop here the argument which Cushny finds in favor of the modern theory, mention may be made of the best experimental evidence supporting it, inasmuch as a portion of it has a clinical significance. For example, he calculates that to produce 1200 c.c. of urine containing 20 grams of urea, 60 liters of blood plasma fluid containing 0.03 per cent urea would have to be filtered through the capsule and 58.8 liters of water returned to the blood by the uriniferous tubules. Since the blood flow through the kidneys is very great, amounting to about 500 liters per day, only about 13 per cent of the fluid contained by the blood passing through the glomerulus would pass by filtration through the capsule of Bowman. This seeming large amount of water which the tubules would have to reabsorb per day is small when it is pointed out that because of the great number of these tubules each would probably not have to reabsorb more than 0.01 c.c. per hour.

The modern theory assumes that the capsule is a filter which allows the deproteinized blood plasma to pass through it into the renal tubes. The passage of the fluids through the membrane would depend upon several factors:

First. The difference in the pressure between the blood and the urinary filtrate. This is furnished by the pressure of the blood in the glomerular vessels.

Second. The character of the membrane of the capsule. The capsule is impervious to the proteins of the blood and pervious to its other constituents.

Third. The character of the blood. If the blood contains a substance which can not pass through the filter and which exerts an osmotic pressure in opposition to the filtering force, it will act to reduce the rate of filtration as well as the amount filtered.

If the capsule acts as a filter it should be possible to alter the rate of urine excretion by varying any of these factors, and such is the case. For example, if the blood pressure be raised by tying off several branches of the aorta, the urine is appreciably increased, or if the blood pressure is decreased, as can be done by compressing the renal artery, the amount of urine is decreased. Increase in blood pressure alone without at the same time increasing the volume flow of blood through the kidney apparently does not increase urine excretion. This is explained by the fact that any notable increase in the concentration of the colloids in the plasma increases the osmotic pressure of the blood which acts in opposition to the pressure of blood in the capillaries. This point was shown a number of years ago by Starling and his pupils who found that the secretion of urine ceases when the capillary pressure in the glomerulus falls below that exerted by the osmotic pressure of the blood proteins, the critical pressure being from 30 to 40 mm. of mercury. They also found that when the osmotic pressure of the blood proteins was reduced by dilution of the blood with saline solution, the rate of excretion was increased; excretion in such cases being maintained at a blood pressure below the normal critical pressure. If the dilution of the blood was made with saline containing gelatin, on the other hand, the diuretic effect was greatly decreased. These experiments indicate that saline produces its diuresis by diluting the plasma proteins and lowering their osmotic pressure. The proof that the capsule acts as a filter appears fairly complete, but no such experimental evidence can be obtained to prove the assumption that the

epithelium of the tubules reabsorbs the excess water and salts which are filtered off through the capsule.

If Cushny's modern theory of excretion is correct, the tubules must absorb not only large amounts of water, but they must allow for the reentrance into the blood, either completely or incompletely, of certain salts while they must reject others entirely.

The urine contains a very high percentage of small molecules, and the proportion in which they are present is entirely different from that found in the blood plasma, and, presumably, in the glomerular filtrate. The following figures give the average normal value for urea, uric acid, chlorine and glucose in 100 c.c. of protein free blood plasma and 100 c.c. of urine, in the third column is given the change in concentration which occurs in the kidney:

	100 C.C. PROTEIN-FREE BLOOD PLASMA CONTAINS	100 C.C. URINE CONTAINS	CHANGE IN CONCENTRATION IN THE KIDNEY
Urea	.033	2.	60
Uric Acid	.0022	.05	22.7
Chlorine	.41	.6	1.5
Glucose	.1	–	-

Here the blood plasma fluid contained but 0.033 per cent of urea, and the urine 2 per cent. Accordingly, 6 liters of glomerular filtrate would be required to furnish 100 c.c. of urine. Six liters of glomerular filtrate would contain 6.6 grams of sugar, 0.132 grams of uric acid, and 24.6 grams of chlorine. But 100 c.c. of urine contains no glucose, 0.05 grams of uric acid and 0.6 grams of chlorine. According to the modern theory, these figures indicate that during the passage of the urine through the tubules 5900 c.c. of water, 6.6 grams of sugar, 24 grams of chlorine and 0.067 grams of uric acid would have to be absorbed by the renal epithelium in the production of 100 c.c. of urine containing the concentration given above.

Among the most convincing experiments that can be offered in support of the absorption of fluid and salts by the tubules are those in which the pressure of the urine in the tubules is slightly increased by partial closure of the ureter (Cushny). In these experiments the ureter of one kidney is partly closed with a clamp and the excretion obtained from this kidney is compared with that of the opposite normal kidney. In general, obstruction of the ureter results in a decrease in the amount of water, chloride and urea excreted. But, curiously, the urea content is decreased relatively less than is the chloride and water content. These results can be explained on the basis that any pressure acting to oppose the head of pressure producing filtration in the glomerulus will reduce the amount of the glomerular filtration, and accordingly the time allowed for the passage of this filtrate along the tubules is increased, and absorption becomes more complete. Since urea is probably not absorbed at all and chloride is, the discrepancy in the effects on the excretion of urea and chlorine in the partially obstructed kidney can be explained.

When very large amounts of water are taken by mouth, it often happens that the urine excreted has a concentration of salts less than that present in the fluid of the blood. Some investigators believe that such a condition is possible

only on the assumption that water is actively excreted, but a more plausible explanation based on the modern theory is that the water that is absorbed from the alimentary tract reaches the kidney as a dilute saline solution, and is rapidly filtered off in a form somewhat more dilute than the optimal solution which blood plasma must have for the well-being of the tissues.

It is impossible to analyze the forces that are responsible for such a degree of absorption by the epithelium of the tubules. For the present we must classify them, for want of a better term, as vital forces. The questions that await immediate investigation are whether absorption actually takes place, and, if it does, what factors cause it to vary. Many attempts have been made, by destroying the capsules or the tubules by means of poisons or by operations to determine directly or indirectly the question of the function of the tubules.

In such experiments, however, the number of factors involved confuse the issue and make the results practically valueless so far as determining the normal function of the tubules. Other experimenters have attempted to show absorption in the tubules by injecting diffusible substances, such as chemicals and dyes, into the ureter under what they deemed sufficient pressure to force the solution into the tubules, and by an examination of the blood or the tissues to determine whether or not the injected substances had been absorbed. The results obtained are not convincing, for it is very questionable whether it is possible to inject a substance into the tubules from the ureter.

Cushny fails to find any evidence for the vital theory of excretion in the supposed ability of the renal cells to excrete dye substances injected intravenously. He points out that all well controlled work has failed to confirm this generally accepted teaching. Cushny gives the accompanying table in which the movements of the concentration of the blood plasma are followed through the kidney. The ultimate destination of each is indicated by the enclosures. It is noted that the dextrose alone is completely absorbed and that the urea and the sulphate are not absorbed at all from the glomerular filtrate. The other salts are partly absorbed.

	67 LITERS PLASMA CONTAIN		62 LITERS FILTRATE CONTAIN IN ALL	61 LITERS REABSORBED FLUID CONTAIN		1 LITER CONTAINS		
	PER CENT	TOTAL		PER CENT	TOTAL	PER CENT	TOTAL	
Water	92	62.1	62.1	—	61.1	95	950	c.c.
Colloids	8	5360 gr	—	—	—	—	—	
Dextrose	0.1	67 gm.	67 gm.	0.11	67 gm.	—	—	
Uric Acid	0.002	1.3 "	1.3 "	0.0013	0.8 "	0.05	0.05	gm.
Sodium	0.3	200 "	200 "	0.32	196.5 "	0.35	3.5	"
Potassium	0.2	13.3 "	13.3 "	0.019	11.8 "	0.15	1.5	"
Chloride	0.37	248 "	248 "	0.40	242 "	0.6	6.0	"
Urea	0.03	20 "	20 "			2.0	2.0	"
Sulphate	0.003	1.8 "	1.8 "			0.18	1.8	"

He points out that Barcroft and Straub have shown that the diuresis which results from the injection of saline into the blood is not accompanied by any in-

crease in the oxygen consumption of the kidney, and that this fact coupled with the fact that the total amount of chloride, urea and sulphate, which is excreted during saline diuresis is greater than under normal conditions indicates that the excretion of these salts is not due to any vital secretory power of the kidney, but rather to factors that are extrarenal in origin.

The diuresis produced by adding urea or sodium sulphate to the blood, on the other hand, is accompanied by an increase in the oxygen consumption of the kidney. This increase can not be due to active elimination of these salts by the tubules, the work of which requires oxygen, for no increase in oxygen consumption accompanies the increased excretion of the same salts under saline diuresis. Sulphate and urea are nonthreshold substances, and are not absorbed by the tubules. The explanation of the oxygen consumption is probably that the osmotic pressure which these bodies in the glomerular filtrate exert makes it necessary for the epithelium to oppose a greater absorbing force to concentrate the urine, and hence a greater expenditure of energy is required.

While the modern theory does not explain the diuretic action of the xanthine compounds, it does allow for the explanation of the polyuria in diabetes, this polyuria being due (1) to the excessive amount of water taken, and (2) to the inability of the kidney to concentrate the urine against the osmotic pressure offered by the concentrated sugar solution in the tubules. In these cases sugar is a nonthreshold substance, so to speak, and none of it is absorbed. The diuretic action of the digitalis group is dependent upon its influence on the circulatory system. The diuretic action of pituitary extract has not been determined in the light of modern theory. The presence of albumin in the urine in nephritis and cardiac failure would be explained by the modern theory as being due to a change in the permeability of the filtering membrane. —*R. G. P.*

*Acute Infectious Jaundice**

EPIDEMICS of jaundice have occurred from time to time in many parts of the world. These epidemics have remained puzzles, so far as their etiology is concerned, until within the past few years, when, following the reports of researches of a group of Japanese investigators, a microbiologic cause was generally recognized. Even yet, despite the fact of comprehensive reports by Inada and his coworkers, and despite the reports from the battle fields of France, Italy, Germany, and Russia, the facts have not made the proper impression in the United States, except in a small group of workers.

In 1917 Noguchi found that rats captured in New York City were infested with a spirochete apparently identical with that causing spirochetal jaundice in men, and identical with the parasite causing the disease in human beings in Europe and Japan. Jobling made similar observations in Nashville, Tenn., and Neill in Washington. Comprehensive evidence has accumulated to the effect that *Spirocheta icterohemorrhagica* is the cause of a type of jaundice and that the organism is disseminated among the wild rats in various parts of the United States.

As has been shown by Neill, spirochetal jaundice is not a new thing in this country. Quite definite reports of the disease among the troops during the war

*A complete bibliography is given in Neill's article in Public Health Reports, May 10, 1918, pp. 717-726, United States Public Health Service, Washington, D. C.

of 1812 have been found. During the Civil War not less than 71,691 cases were reported among the white troops of the Union Army. Sometimes these cases were sporadic; sometimes they were locally epidemic. While in some instances the cases seemed to be related in some way to malaria, in others the accounts are clear enough to make it almost, if not entirely, certain that the outbreaks were due to the same disease that in later years has been observed in the trenches of European battle fields, but the disease has not been confined to the trenches. It has been reported not infrequently in civil populations.

In all the American reports most of the patients have been described as suffering from nausea or vomiting, some abdominal distress or pain, headache, and fever in varying degrees, followed within a few days by jaundice of different grades in different cases. In fact, says Neill, from many of the descriptions there is little to suggest a specific infectious disease, aside from the fact that a number of cases would appear about the same time in a community which previously and subsequently was free from the disease. Several reports indicate a high mortality among pregnant women. In some outbreaks children seem to have been relatively more frequently attacked than adults, and in others adults were most often subjects of the disease. In some outbreaks males were principally affected, in others the sex incidence was equally divided. In several outbreaks the symptomatology in the fatal cases was strikingly similar and suggestive of rapid necrosis of the liver cells as occurs in acute yellow atrophy.

There is some evidence that direct contact has played a part in transmission.

The starting point of most at least of the outbreaks of infectious jaundice seems to have been the rat, and Noguchi says of this that the finding of the causative agent of infectious jaundice among the wild rats in America, and the identification of this strain with those found in Asia and Europe seems to be particularly important in revealing a latent danger to which we have been constantly exposed, but from which we escape as long as sanitary conditions are not disturbed by untoward events.

Long before the present war acute infectious jaundice was known to occur especially among troops, in sewer workers, in agricultural workers digging in wet soil, and in miners. Persons who handle foods, as butlers and cooks (in Japan at least) are also said to be attacked with especial frequency. While the problem of the rat in relation to this disease has not been completely worked out, the following statement of the mode of transfer forms a reasonable hypothesis: About 10 per cent of all wild rats, wherever located, probably carry the spirochete in their kidneys and excrete them in their urine. If this organism finds a favorable environment in the soil, a sufficient number may live long enough to infect a person who gets them into his mouth or on his skin.

Diagnosis may be made by staining blood films with Romanowsky stains or by one of the impregnation methods; by examination of blood by the dark-field method; and by injection of blood into the peritoneal cavity of a guinea pig. If the spirochetes are present the pig will sicken and die in about ten days, and postmortem will show a combination of hemorrhage and jaundice which is almost pathognomonic. Other methods are microscopic examination of centrifugalized urine sediment stained properly; injection of urine sediment into guinea pigs; and examination of tissues, especially kidney, after staining by the Levaditi method.

—*P. G. W.*

Concerning Medical Manuscripts by Medical Officers

AS stated in the circular memoranda for Editors of Medical Publications issued by the Surgeon General's Office on March 27th and May 22, 1918, it is required by paragraph 423, Manual of the Medical Department, that all medical manuscripts by medical officers, U. S. Army, intended for publication shall be first submitted to the Surgeon General's Office, Washington, D. C., for approval. This regulation, which has been very courteously complied with, to date, is still in force as far as medical officers on active duty are concerned. In the case of medical officers recently retired from active duty, it is requested, as a courtesy to the Surgeon General and in aid of assembling material for the Medical History of the War, that all medical manuscripts based upon military or official records or upon military experience during the War, be submitted as heretofore, to the Secretary, Board of Publications, Surgeon General's Office, Washington, D. C., for record and approval and that such MSS be accompanied by a carbon copy. Upon approval, the original copy will be forwarded to the journal designated, for publication, and the carbon will be filed in the records of the Medical History of the War.

For the Surgeon General:

(Signed) C. R. Darnall, Colonel, Medical Corps,
U. S. A., Executive Officer.

U. S. Interdepartmental Social Hygiene Board

THE United States Interdepartmental Social Hygiene Board, through its Executive Secretary, Dr. T. A. Storey, 1800 Virginia Avenue, N. W., Washington, D. C., announces the following appropriations from the Scientific Research Fund of the Board:

Leland Stanford Junior University Medical School.

(1) "Investigation into more effective treatment in acute and chronic gonorrhea," under the direction of R. L. Rigdon, M.D., Clinical Professor of Genito-urinary Surgery, and A. B. Spalding, M.D., Professor of Obstetrics and Gynecology $2,300

(2) "The permeability of the meninges to anti-syphilitic drugs—an attempt to increase their permeability," under the direction of H. G. Mehrtens, M.D., Clinical Professor of Neurology 2,300

(3) "Investigation into more effective methods of treating syphilis," under the direction of H. E. Alderson, M.D., Clinical Professor of Dermatology 2,600

Total $7,200

University of Michigan, College of Medicine and Surgery.

(1) "A research for an improved method of demonstrating the spirochaeta pallida in human tissues," under the direction of A. S. Warthin, M.D., Professor of Pathology $6,000

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ORIGINAL ARTICLES

CLINICAL OBSERVATIONS CONCERNING THE FRAGILITY OF ERYTHROCYTES*

By H. Z. Giffin, M.D., and A. H. Sanford, M.D., Mayo Clinic, Rochester, Minn.

ALTHOUGH many early studies concerning hemolysis had previously been made, Ribierre in his Paris thesis, published in 1903, was the first to clearly summarize the knowledge concerning corpuscular resistance and to devise a clinical method of practical value for the measurement of the resistance and fragility of erythrocytes. The methods formerly proposed required the use of more blood than could be obtained ordinarily for routine clinical work. Ribierre's method, however, is simple and with various modifications is in general use today. In his Paris thesis Ribierre discussed the existing knowledge concerning the various globulicidal agents and the mechanism of hemolysis, the different methods proposed for the measurement of resistance, and elaborated his own method. He studied especially and in detail, the increased resistance found in the different types of jaundice and endeavored to interpret the cause of this increased resistance.

It is a very curious fact that in Ribierre's exhaustive study of resistance in jaundice he should have overlooked the most important diagnostic discovery in connection with the subject. In other words, he failed to demonstrate the decreased resistance or rather increased fragility so constantly present in hemolytic jaundice.

*Presented before the American Society for Clinical Investigation, May 6, 1918, Atlantic City.

It remained for Chauffard, in 1907, to discover the fact that the erythrocytes in the peripheral circulation of patients with hemolytic jaundice, were abnormal, especially that they were more fragile. This finding has been corroborated in all later reports on the subject.

The use of hemolytic serums or of mechanical methods for testing the resistance of erythrocytes has not as yet proved of practical value and it is necessary to rely on an estimation of their resistance toward distilled water in hypisotonic salt solution.

Butler has published an exhaustive study on fragility of the red blood corpuscles. Daily examinations of his own blood over a period of months demonstrated that the degree of fragility was constant from day to day and that readings made at different times of the day were the same. His experiments showed that cells washed in salt solution were slightly more fragile, while cells washed in citrated saline were not affected by the procedure. Cells treated by oxygen were more resistant, while those treated by carbon dioxide were more fragile. He emphasized the fact that if comparable results are to be obtained by different workers, a constant dilution (1 to 10 by his method) of the blood must be used. Butler's readings for normal and his results on patients correspond in most instances with our own experience, although his method is different and our dilutions are approximately 1 to 25.

Hill obtained high readings as a result of the use of washed corpuscles. Davis concluded that he obtained less uniform results with washed corpuscles. Hill also demonstrated that the use of arsenic increased the resistance and that splenectomy lowered the point of complete hemolysis.

A word should be said concerning the importance in our own experience, of a control test in the estimation of fragility. The control test furnishes a method of determination of the accuracy of the salt solution used. Moreover with the use of a fixed normal, for example, of 0.34 per cent for maximal resistance, smaller variations in resistance can not be accurately interpreted. With the use of a control a variation of from 0.02 per cent to 0.04 per cent may be regarded as quite definite. In this way the use of a control test furnishes a better method of comparison and interpretation, in addition to its value as a test of the accuracy of the salt solution itself.

TECHNIC OF TEST FOR FRAGILITY OF ERYTHROCYTES

A review of the literature of diseases marked by blood destruction impresses one with the fact that there has been no uniformity in the various methods used in studying the fragility of the red blood cells.

The use of saponin need not be considered in connection with the present study. The work of M'Neil seems to indicate that a study of fragility with this hemolytic agent does not give results conforming in all respects to those obtained with hypisotonic salt solutions.

Most methods of testing the fragility of erythrocytes depend on the observation of the breaking up of the cells in salt solutions of various percentage strength, the chief difference lying in the method of making the various solutions, and of reading and reporting end-points, or degrees of hemolysis.

Karsner and Pearce employed Theobald Smith's method as modified by Gay. "Chemically pure sodium chloride was dried for two hours at 170° C. and immediately weighed in amounts necessary to make 500 c.c. volumes of salt solution ranging from 0.1 to 0.5 per cent in steps of 0.25 per cent. In order to be sure of approximately the same volume of corpuscles in the anemic as in the normal bloods, the gently defibrinated blood was centrifuged and the serum drawn off. One-tenth centimeter of the corpuscular mass was measured in a graduated pipette and placed in 3 c.c. of each of the various salt solutions. Standard colorimetric scales for comparison were made by laking red cells with distilled water; thus the laking of 0.4 c.c. of the corpuscular mass in 12 c.c. of distilled water represented a standard of 100 per cent hemolysis. Dilutions of this solution were made so as to have tubes showing the color values of 80, 60, 40, and 20 per cent hemolysis." Preliminary readings were made, and the mixtures placed in the incubator for eighteen hours when the results were finally read.

Butler describes his technic in detail. The essential difference in his method from others is in the manner of making his mixtures of blood and saline. He uses a Wright capillary pipette of fine bore with an arbitrary unit of measurement marked on the capillary portion of the tube. This small pipette is used for measuring nine units of saline solution of definite percentage strength into a miniature test tube made from ¼-inch glass tubing cut off in 1½-inch lengths and sealed at one end. This procedure is repeated using each one of the different stock saline solutions made fresh each day from a stock 1 per cent sodium chloride solution. Butler uses a burette for making dilutions of 1 per cent sodium chloride with distilled water in intervals of strength of 0.025 per cent. Generally the range employed is from 0.45 per cent to 0.30 per cent. In a few instances the strongest solution is 0.7 per cent. A single unit of blood drawn in the Wright pipette from a puncture of the thumb, is added to each of the small test tubes containing nine units of saline, so that his final mixture is always 1 to 10.

Hill has recently reported a method in which he used a definite amount of washed corpuscles (0.05 c.c.) in hypisotonic salt solutions of different percentages.

The method of Ribierre has seemed to us to be the most satisfactory simple method for accurately determining the fragility of erythrocytes. This author uses a stock solution of 0.5 per cent sodium chloride. In a series of small test tubes he places different amounts of this stock solution; in the first tube 50 drops, in the second 48, in the third 46, etc. To each tube is then added the number of drops of distilled water necessary to make the total volume of solution in each tube 50 drops. A definite amount of blood (20 cm.) measured with a graduated capillary pipette is added to each tube of solution. The various degrees of hemolysis from "slight" to "complete" are noted. Normally, hemolysis begins in the tube containing 44 drops of 0.5 per cent salt solution. The percentage of salt in this tube is 44/50 of 0.5 per cent, or 0.44 per cent. Our own modification of this method in detail is as follows:

The stock solution is made by dissolving 0.5 gm. sodium chloride (chemi-

Fig. 1.—Dilutions are made of 5 per cent sodium chloride solution by adding distilled water by the drop method, so that each tube contains twenty-five drops of hypisotonic solution.

Fig. 2.—One drop of whole blood is added to each tube of hypisotonic solution.

cally pure and anhydrous) in 100 c.c. distilled water. Great care should be exercised in making this solution. A good balance must be used for weighing the salt, and a volumetric flask employed for measuring the water.

A twelve hole Wassermann rack, with at least two rows of holes, is filled with three-inch by three-eighths-inch tubes. The front row is for the patient's test, the back row for a control. The tubes in the front row are numbered with a glass marking-pencil, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, and 14. In each tube in the front row, and in the tube in the back row immediately behind it, is placed the number of drops of 0.5 per cent salt solution indicated by the figure marked on the tube in the front row. A capillary pipette drawn from soft glass tubing is used for putting the drops of salt solution in the tubes. With the same pipette distilled water is added drop by drop to each tube so that there is a total of 25 drops; for example a tube marked "20" should contain 20 drops of 0.5 per cent sodium chloride solution and 5 drops of distilled water, and the tube immediately behind it (control tube) should contain the same.

The patient is bled by puncturing the vein in the usual manner for obtaining blood for a Wassermann test. A rather small gauge needle should be used, and there should be no delay in getting the blood. An all glass syringe, sterilized by boiling, and thoroughly dried should be used. It is not necessary to rinse out with normal salt solution, in fact it would not be advisable as in this way an excess of salt might be added to the solutions in the tubes. One drop of blood should be allowed to fall into each tube of the front row. The tube should be thoroughly shaken to make an immediate corpuscle suspension. The plasma is greatly diluted and usually no fibrin is formed. If a slight clot forms it should be free from corpuscles.

In the back row (control tubes) should be placed blood obtained in a similar manner from a normal person. It may seem unnecessary to use a control in every test. In fact if several patients are being tested at one time, one control serves for all. The purpose of this test of normal blood is to insure that the salt solution is of the proper strength, as of course a very slight alteration makes a difference in the result. Every patient's blood, then, is considered not only in relation to the different strengths of salt solution determined by reckoning the dilutions in each tube, but also is compared with the behavior of supposedly normal corpuscles in solutions of exactly the same strength.

The tubes are allowed to stand an hour or two at room temperature and the results are then read. The dilution in which there is just a slight tingeing of the supernatant fluid due to the laking of a few of the least resistant corpuscles is noted as the point of initial hemolysis. Reading from left to right, the first tube in which it can be demonstrated that the hemoglobin is entirely free, and that there is no corpuscular residue evident by shaking the tube, indicates the point of complete hemolysis. The percentages of salt solution indicative of initial and complete hemolysis are readily reckoned; that is:

Tube marked 20 showing beginning hemolysis contains 20 25 of 0.5 per cent sodium chloride = 0.40 per cent sodium chloride.

Tube marked 16 showing complete hemolysis contains 16 25 of 0.5 per cent sodium chloride = 0.32 per cent sodium chloride.

The percentage can be immediately determined by multiplying the number on the tube by 0.02. Normal blood shows beginning hemolysis in 0.42 per cent to 0.38 per cent sodium chloride solutions and hemolysis to be complete in solutions of 0.36 per cent to 0.32 per cent sodium chloride. When initial and complete hemolysis occur in solutions stronger than normal an "increase of fragility" is present. When hemolysis occurs only in solutions weaker than those which lake normal blood, the cells under observation are more resistant than normal and such blood is reported as having an "increase of resistance."

It seems to us important to use chiefly the expressions "initial hemolysis," "complete hemolysis," "increase of fragility," and "increase of resistance" in order to obviate the confusion of terms which is apt to occur in a discussion of this subject.

CLINICAL RESULTS

We have had an opportunity to study a comparatively large group of cases of hemolytic jaundice, pernicious anemia, splenic anemia and myelocytic leucemia with respect to fragility, and the results, although largely of corroborative value, demonstrate certain interesting details.

TABLE I

FRAGILITY TESTS IN HEMOLYTIC JAUNDICE

Twenty-three Nonoperative and Preoperative Cases

CASE	*Percentage NaCl*				REMARKS
	INITIAL CONTROL	HEMOLYSIS PATIENT	COMPLETE CONTROL	HEMOLYSIS PATIENT	
86218			.42	.46	
135948			.34	.40	
141268			.34	.40	
153245			.38	.46	
148209			.36	.40	Brother complete .42.
			.42	.44	
161538			.38	.44	
162670			.36	.40	
94675			.38	.44	
91298			.32	.40	
			.36	.40	
153653			.36	.42	Mother complete at .40½ Nonoperative.
157525			.35	.38	Mother complete at .42. Nonoperative.
169405			.36	.42	No operation.
172287			.38	.42	Mild. No operation.
			.36	.42	
216019				.44	No operation.
205552			.36	.42	Father .46 — .40.
			.38	.40	
	.44	.46	.36	.38	
187817	.46	.50	.38	.46	No operation.
216591	.42	.46	.34	.38	
192817	.44	.50	.36	.42	
211816	.42	.48	.34	.40	
212273		.50		.40	Father .50 — .42.
190364		.46		.40	
190774		.50		.38	
	.44	.50	.34	.40	
212934	.46	.42	.36	.36	
Averages	.44	.478	.363	.412	

Hemolytic Jaundice, (25 Cases, Tables I, II, and III). The fragility of erythrocytes has been estimated in twenty-five patients with hemolytic jaundice. These were all definite cases although some of them were mild. In twenty-three nonoperative and preoperative cases twenty-nine tests were made; in all but three there was a markedly increased fragility. In two of these three the point of complete hemolysis was 0.02 per cent higher than the controls. In one only of the entire group could the fragility be said to be normal; this was in a very mild but, from all standpoints, a definite case. It is an important fact that no case which from a clinical or surgical standpoint could be diagnosticated as primary hemolytic jaundice, showed an increase of resistance. The fact that hemolytic jaundice may occur with normal fragility is corroborated; but it is possible that observations at other times would show in the same patient an increased fragility. It is also probable that the increased fragility of hemolytic

TABLE II

FRAGILITY TESTS IN HEMOLYTIC JAUNDICE AFTER SPLENECTOMY (12 CASES)

CASE	*Percentage NaCl*				TIME AFTER SPLENECTOMY
	INITIAL CONTROL	HEMOLYSIS PATIENT	COMPLETE CONTROL	HEMOLYSIS PATIENT	
112836			.34	.40	1 year 8 months.
			.36	.48	1 year 9 months.
141268			.36	.46	18 days.
142074			.38	.42	15 days.
153245			.34	.42	1 month.
148209			.36	.36	23 days.
			.36	.40	4 months.
	.42	.42	.36	.36	1 year 2 months.
161538			.34	.40	21 days.
162670			.32	.42	22 days.
			.36	.40	2 months.
	.42	.50	.32	.36	1 year 8 months.
94675			.32	.32	1 month.
216591	.44	.50	.32	.38	22 days.
190364	.46	.50	.36	.40	18 days.
192817	.38	.50	.32	.36	24 days.
212273	.46	.50	.34	.40	19 days.
Averages	.43	.486	.344	.396	

TABLE III

FRAGILITY TESTS—HEMOLYTIC JAUNDICE

	General Averages—Percentage NaCl			
	INITIAL CONTROL	HEMOLYSIS PATIENT	COMPLETE CONTROL	HEMOLYSIS PATIENT
23 cases nonoperative and preoperative	.44	.478	.363	.412
12 cases postoperative (splenectomy)	.43	.486	.344	.396
10 cases preoperative	.43	.48	.363	.414
Same 10 cases postoperative	.43	.486	.34	.39

jaundice can be modified by long continued anemia and by a concurrent septic process even to the degree that an increase of resistance may be present.

The relatives of four patients with hemolytic jaundice were found to have an increased fragility, in two instances the father, in one the mother, and in another a brother. Two of these four relatives had no symptoms whatever of the disease, and in two of them the symptoms were first noted at the age of eighteen and twenty years. This would seem to indicate a definite hereditary factor even in cases in which an onset occurs in later life.

The averages in hemolytic jaundice for initial hemolysis were, controls 0.44 per cent, patients 0.478 per cent. The averages for complete hemolysis were controls 0.365 per cent, patients 0.413 per cent. The point of highest initial hemolysis was 0.50 per cent, the point of highest complete hemolysis was 0.46 per cent.

After splenectomy (Table II) for hemolytic jaundice seventeen tests were made in twelve cases. In general an increased fragility was present in estimations made fifteen days to one year and nine months after splenectomy. There was, however, a definite, although slight decrease of fragility with respect to complete hemolysis, although only two patients showed a normal resistance. One patient who had in all six tests, gave a return to normal for both initial and complete hemolysis one year and two months following operation. The point of initial hemolysis did not, however, show this definite shift toward normal after splenectomy.

The averages after splenectomy for hemolytic jaundice were for initial hemolysis controls, 0.43 per cent, patients 0.486 per cent. The averages for complete hemolysis were controls 0.344 per cent, patients 0.396 per cent.

In a total of 260 tests on 225 patients a definite increase in fragility, 0.04 per cent or more, was found in only four cases which were not hemolytic jaundice. This is no greater number than would be accounted for by errors of technic. These cases were, respectively, an acute lymphatic leucemia, a lymphosarcoma, an inoperable carcinoma of the stomach, and an indefinite case with splenomegaly and arthritis. Increased fragility in cases with cyanosis has been noted by others in a few instances. By these observations the value of the fragility test in the diagnosis of hemolytic jaundice is conversely demonstrated; that is the finding of a definite increase of fragility is almost certain evidence of the existence of hemolytic jaundice.

Butler has shown that both washed (sodium chloride) and unwashed corpuscles of patients with hemolytic jaundice show an increased fragility; and that, as with normal cells, oxygen increases their resistance slightly while carbon dioxide increases their fragility. He reports six cases occurring in two families. Davis corroborates the findings with respect to washed corpuscles.

Myelocytic and Lymphocytic Leucemia.—The resistance of the erythrocytes is shown to be normal in myelocytic leucemia (12 cases, Table IV). There may be a slight general tendency toward an increase of resistance, but this is not of a definite nature. The averages were, for initial hemolysis, controls 0.42, patients 0.436, for complete hemolysis controls 0.348, patients 0.333. Patients were tested before and after the application of radium over the spleen and it

was thought in two instances that an increased fragility followed the use of radium. This observation did not, however, prove to be constant. Three cases

TABLE IV

FRAGILITY TEST—MYELOCYTIC LEUCEMIA (12 CASES)

CASE	MINIMUM RESISTANCE CONTROL	MINIMUM RESISTANCE PATIENT	MAXIMUM RESISTANCE CONTROL	MAXIMUM RESISTANCE PATIENT	DATE
173747	....	....	.36	.36	10- 2-16
180499	....	.46	....	.38	5- 9-17
173740	....	....	.36	.36	10- 2-16
221207	....	.46	....	.34	2-12-18
194399	.44	.42	.36	.34	5-16-17
221664	.40	.46	.32	.36	2-11-18
	.42	.46	.36	.34	2-15-18
173772	....	....	....	.34	9-29-16
194933	.42	.42	.34	.30	5-28-17
207035	.46	.46	.38	.32	9- 6-17
220165	.46	.40	.34	.30	2-12-18
	.42	.44	.36	.34	1-28-18
168742	....	....	.34	.34	8-22-16
	....	....	.36	.28	2- 2-17
192150	.34	.38	.30	.30	4-28-17
Averages	.42	.436	.348	.333	

of lymphocytic leucemia were tested, two of them showed normal resistance and one, an acute case, a slight increase of fragility. Butler noted normal fragility in two cases of myelemia and one of lymphemia.

Splenic Anemia (14 Cases, Table V).—The cases of splenic anemia in this group were carefully selected. Identifiable cases of chronic septic splenomegaly, luetic splenomegaly, cirrhosis of the liver and, so far as possible, all of those diseases which have been so commonly confused with splenic anemia in the literature were excluded. In most of the cases of splenic anemia a definite increased resistance was shown. The averages for the fourteen cases were, for initial hemolysis controls 0.438, patients 0.402. Complete hemolysis controls 0.353, patients 0.316, with an average hemoglobin of 44 per cent. There seemed to be still more definite increase of resistance following splenectomy.

Karsner and Pearce have demonstrated an increase of resistance experimentally following splenectomy in animals; it occurred in association with the anemia, apparently due to splenectomy. The increased resistance following splenectomy for splenic anemia in man occurs without apparent relationship to the already existent anemia. One patient showed complete hemolysis, less than 0.28 per cent, two years and ten months after operation. The increased resistance in cases of splenic anemia preceding splenectomy may be entirely secondary to the chronic anemia. There is, however, a similarity to the increased resistance of cases of portal cirrhosis in which anemia of a definite degree has never been present. Hill found normal fragility in two cases of splenic anemia.

Pernicious Anemia (18 Cases, Table VI).—Although pernicious anemia has certain features that are similar to hemolytic jaundice, there is no similarity in

the behavior of the erythrocytes to hypisotonic salt solution. The resistance of the red cells is usually definitely increased in pernicious anemia although in some of the cases it is normal. The averages for eighteen cases were, for initial

TABLE V

FRAGILITY TEST IN SPLENIC ANEMIA (14 CASES)

CASE	*Percentage NaCl*				Hb.	R. B. C. IN MILLIONS
	INITIAL CONTROL	HEMOLYSIS PATIENT	COMPLETE CONTROL	HEMOLYSIS PATIENT		
224466	.40	.44	.34	.36	52	3.16
161083			.36	.36	50	4.54
165779			.34	.34	34	3.46
158085			.36	.36	45	3.33
214034	.44	.38	.38	.30	52	3.28
		.38		.28		
167319			.30	.30	73	4.91
216004		.42		.32	38	2.57
214146	.42	.40	.34	.30	26	2.38
144914	.42	.42	.34	.34	63	3.52
215670	.46	.42	.36	.34	15	1.57
191277	.44	.44	.36	.30	62	3.96
	.42	.40	.34	.28 —	45	3.77
209234	.48	.42	.38	.32	20	2.54
119565	.44	.30	.38	.28 —	30	2.08
129358	.46	.40	.36	.28	60	4.3
Averages	.438	.402	.353	.316	44.3	3.28

TABLE VI

FRAGILITY TEST IN PERNICIOUS ANEMIA (18 CASES)

CASE	*Percentage NaCl*				Hb.	R. B. C. IN MILLIONS	TIME AFTER SPLENECTOMY
	INITIAL CONTROL	HEMOLYSIS PATIENT	COMPLETE CONTROL	HEMOLYSIS PATIENT			
188649	.44	.40	.36	.32	55	2.49	
212480	.44	.38	.38	.34	33	1.33	
139695			.36	.28	30	1.78	7 months.
158136			.36	.30	28	1.51	7 weeks.
162242			.34	.24	50	1.9	
220132	.42	.40	.36	.32	43	1.67	
151088			.36	.30	41	1.98	4 months.
153395			.32	.30	75	3.81	3 months.
157290			.32	.30	84	5.2	18 days.
188717			.38	.36	30	1.31	
197254	.42	.42	.36	.36	40	1.51	
181414			.36	.36	19	1.03	
160970			.38	.32	50	2.57	
170115			.36	.36	39	2.44	
129968				.32	71	2.6	3 weeks.
164775			.34	.34	29	1.9	
196267	.42	.44	.32	.34	33	1.74	
124257			.38	.34	68	4.28	3 months
Averages	.428	.408	.355	.322	45.4	2.28	

hemolysis, controls 0.428, patients 0.408, complete hemolysis controls 0.355, patients 0.322, with the hemoglobin averaging 45 per cent and the red cell count 2,280,000. It is possible that the increase of resistance has been due to the chronic anemia present.

Again, as with splenic anemia, the resistance of erythrocytes is increased quite definitely after splenectomy. This fact I believe has not been previously shown so clearly in any other series of cases.

Hill, using washed corpuscles, found that fragility in thirteen cases of per-

TABLE VII

FRAGILITY TESTS IN PURPURA (4 CASES)

CASE	*Percentage NaCl*			
	INITIAL CONTROL	HEMOLYSIS PATIENT	COMPLETE CONTROL	HEMOLYSIS PATIENT
12155	.46	.46	.34	.34
212138	.46	.44	.36	.36
214778	.42	.42	.34	.34
228359	.40	.40	.32	.32
Averages	.435	.43	.34	.34

TABLE VIII

FRAGILITY IN ANEMIA OF SECONDARY TYPE (11 CASES)

CASE	*Percentage NaCl*				Hb.	R. B. C. IN MILLIONS	REMARKS
	INITIAL CONTROL	HEMOLYSIS PATIENT	COMPLETE CONTROL	HEMOLYSIS PATIENT			
212144		.42		.34	45	3.99	Colitis.
156102			.34	.28	29	3.68	Ulcer.
221504	.44	.40	.36	.28	30	3.71	Ovarian cyst.
179009			.38	.30	28	2.6	Cellulitis.
166483			.32	.32	39	3.52	Myomas.
162653			.34	.24	29	2.38	Hemorrhoids.
210376	.46	.46	.38	.30	42	4.0	Hemorrhoids.
195342	.42	.42	.32	.28	35	3.04	Colitis.
159417			.34	.34	38	3.99	Myomas.
208004	.44	.44	.36	.34	37	3.56	Hematuria.
221439	.38	.40	.34	.32	48	2.97	Sepsis.
Averages	.425	.424	.349	.308	38.3	3.503	

nicious anemia was either high, low or normal, while Davis' findings more nearly agree with ours in that they demonstrate usually an increased resistance.

Purpura (4 Cases, Table VII).—Fragility tests in four patients with severe forms of purpura demonstrate normal values. There is no variation whatever from normal and although the series is small, the results are sufficiently definite to be indicative. Butler obtained normal readings in one case of purpura.

Severe Anemia of Secondary Type (11 Cases, Table VIII.)—Anemia of low color index, whether due to hemorrhage or a chronic infectious process, is

most apt to be associated with an increased resistance of the erythrocytes. Normal resistance is seen in some instances, but the averages show a fall of 0.04 per cent for complete hemolysis. The degree of anemia bears a relationship in most of the cases to the increase of resistance. The readings are quite comparable to those of pernicious anemia. Similar conclusions were drawn by Hill.

Chronic Obstructive Jaundice (12 Cases, Table IX).—The averages obtained in cases with chronic jaundice of the obstructive type are, for initial hemolysis 0.396 per cent and for complete hemolysis 0.31 per cent. A definite increase in resistance is demonstrated. Certain cases of chronic obstructive

Table IX

Fragility Test in Chronic Obstructive Jaundice (12 Cases)

Case	Percentage NaCl				Remarks
	Initial control	Hemolysis patient	Complete control	Hemolysis patient	
206433	.40	.40	.32	.32	No operation; probable cancer, gall bladder and chronic jaundice (3).
157154			.30	.30	Stone common duct, jaundice (3) 3 months.
167420			.32	.32	Biliary cirrhosis, splenectomy, jaundice (3).
189394	.46	.42	.36	.32	Stones, G. B., pancreatitis, cirrhosis, jaundice (2).
156252			.36	.28	Cirrhosis of liver, ascites, jaundice (2), 1 year.
170914			.36	.28	Chr. pancreatitis common duct, obstructive jaundice (3), 6 weeks.
217651	.42	.36	.36	.18	Carcinoma (?), pancreas, jaundice (2), 1 month.
223891	.42	.38	.32	.28	Sandy muddy material common duct, jaundice (2).
180780			.32	.28	Subacute pancreatitis, cancer (?), Hypertrophic cirrhosis.
192980	.44	.42	.36	.28	Stones in gall bladder, suppurative cholangitis, pruritis.
210429	.48	.40	.38	.28	Traum. strict. common duct, complete closure, jaundice.
201168				.28—	No operation, jaundice (2), 1 year, gall bladder, enlarged liver.
Averages	.436	.396	.342	.31	

jaundice give approximately normal readings, but in the large majority of instances resistance is markedly increased. Whether this is due entirely to the jaundice or also to factors present as a result of complications, can not be determined. There is some reason to conclude that chronic septic and toxic processes, as well as bile pigments, increase the resistance of erythrocytes, and it is probable that cirrhosis of the liver, pancreatitis and gall bladder and duct infections, as well as the jaundice itself, may be factors affecting corpuscular resistance. Ribierre's thesis contains a most interesting study of the factors affecting fragility in obstructive jaundice. Subsequent observers have corroborated his clinical findings.

We have not reported in this paper the results on a large number of

miscellaneous cases. Conclusions may be drawn only when a group of cases has been studied; isolated findings may be misleading (Table X).

SUMMARY

A total of 260 tests in 225 cases is the basis for this report. A modified and somewhat simplified Ribierre method has been used.

1. Twenty-five patients with hemolytic jaundice were examined. In all but three there was a markedly increased fragility. Two of these three showed an increased fragility of 0.02 per cent. In only one could the resistance be said to be normal. Of the entire group of 225 cases there were only four with definitely increased fragility in which a diagnosis of hemolytic jaundice could not be made. Relatives of four patients with hemolytic jaundice were found to have an increased fragility; two of these four relatives had no symptoms of the disease, and in the patients themselves the onset of the disease dated to the age of eighteen or twenty years, indicating a hereditary factor even though the onset was late. After splenectomy there was found a slight decrease in the degree of fragility, especially with respect to initial hemolysis.

2. Twelve cases of myelocytic leucemia showed normal fragility with very slight variations toward increased resistance.

3. In fourteen cases of splenic anemia, excluding so far as possible all those conditions so commonly confused with splenic anemia, a definitely increased resistance of erythrocytes was shown. A still greater increase of resistance was demonstrated after splenectomy.

4. In pernicious anemia (18 cases) the resistance of erythrocytes was slightly increased. Here again after splenectomy there was a more definite increase of resistance.

5. Four cases of severe purpura showed a strikingly normal hemolysis without variations.

TABLE X

FRAGILITY OF ERYTHROCYTES

	NUMBER CASES	*Percentage NaCl*			
		AVERAGES		AVERAGES	
		INITIAL CONTROL	HEMOLYSIS PATIENT	COMPLETE CONTROL	HEMOLYSIS PATIENT
Hemolytic jaundice (non-operative and preoperative)	23	.44	.478	.363	.412
Hemolytic jaundice (after splenectomy)	12	.43	.486	.344	.396
Myelocytic leucemia	12	.42	.436	.348	.333
Splenic anemia	14	.438	.402	.353	.316
Pernicious anemia	18	.428	.408	.355	.322
Purpura	4	.435	.43	.34	.34
Secondary anemia	11	.425	.424	.349	.308
Chronic obstructive jaundice	12	.436	.396	.342	.31

6. Anemia of low color index, whether due to hemorrhage or to chronic sepsis, was accompanied by an increase of resistance.

7. In eleven cases of chronic obstructive jaundice in general an increase of resistance was shown.

The test for fragility of erythrocytes in hypisotonic salt solution is of definite practical value especially in the diagnosis of all those diseases which may simulate hemolytic jaundice. It is more accurate when compared with a control test of normal blood.

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SOME STUDIES IN PLASMOGENESIS*

By Alphonso L. Herrera, Mexico City, Mexico.†

I HAVE proposed the name "Plasmogenesis" to cover that group of studies which has existed since the time of Dutrochet's first investigations dealing with the origin of protoplasm. For more than twenty years past I have done work in this field, which with that of Traube, Leduc, Bütschli, Quincke, Harting, Slack, Fischer, and others, now makes up a voluminous literature.[1] The science covers not only the attempts which have been made to reproduce the forms of cells and of lower organisms, but all those at the synthesis of albumins, ferments, lipoids, etc.

My personal endeavors have been directed to the problem of producing artificial cells intended to mimic as perfectly as possible the structures of nature. My first experiments were made with organic substances like tannin, oleic acid,

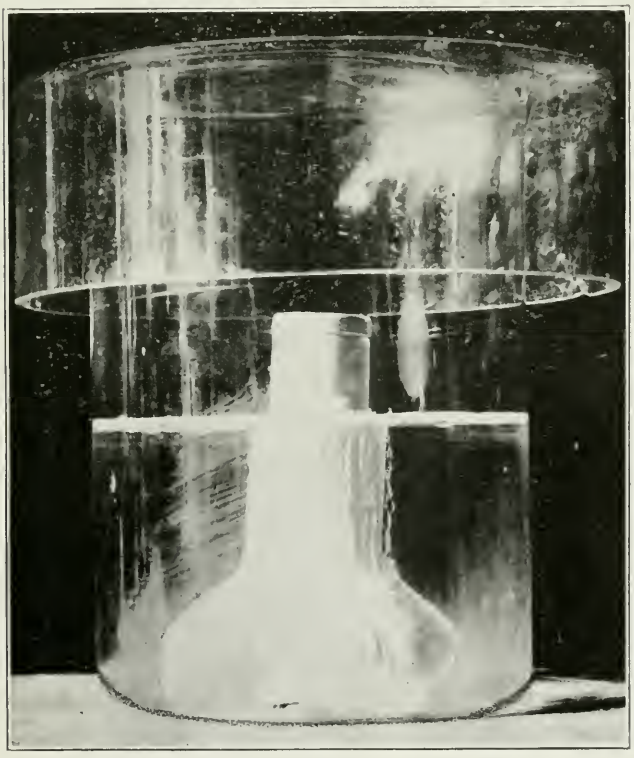

Fig. 1

Fig. 2

albumin and fats. I soon noticed, however, that some of my best results were dependent upon the presence of mineral impurities in the substances employed, more particularly soluble silicates, which with certain salts like calcium chloride

*Translated from the Spanish by Daric Gutiérrez-Laserna of Bogata, Colombia, S. A.

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produce precipitation membranes. During the past years, I have bestowed intensive study upon the artificial forms shown by such silicate precipitates.[2]

Careful investigation has shown me that colloid silicic acid and the colloid silicates yield structures most like natural forms when produced from reaction

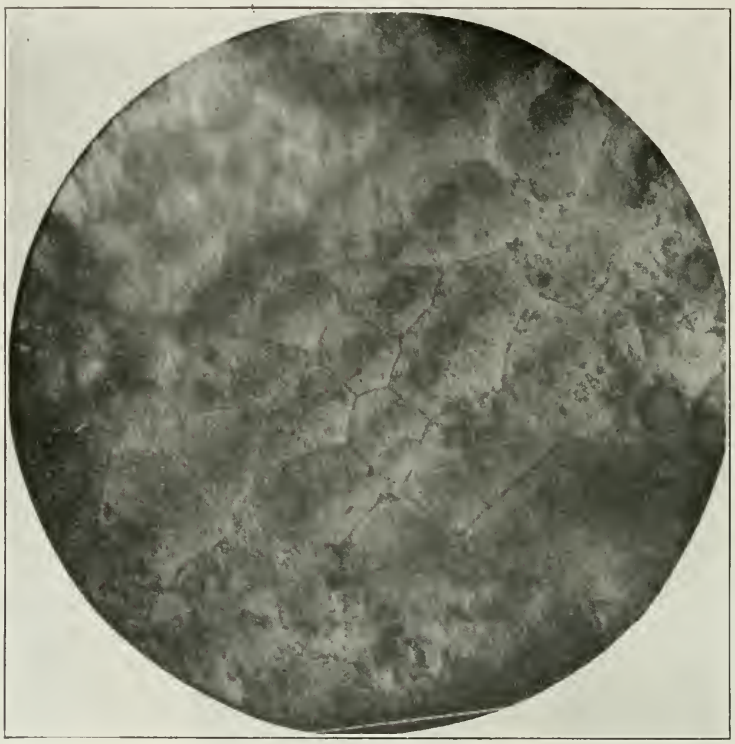

Fig. 3

Fig. 4

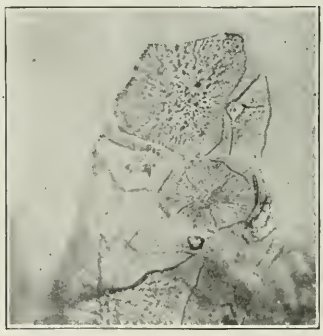

Fig. 5

mixtures of very low concentration, when contact between the precipitating agents is slow and when viscosity of the reacting solutions is great.

In 1917 I observed that the employment of double salts capable of entering into double decomposition with a second salt, yielded mixtures of crystalloid and colloid which mimic in wonderful fashion cells and other organized forms such

as amebæ. To produce these structures I began with a saturated solution of potassium silicate which had been saturated with potassium carbonate. A drop of this was placed on a slide and this covered with a second of calcium chloride. When the solution of potassium silico-carbonate had a sufficient concentration (a specific gravity over 1580), crystals of potassium chloride began to separate out, which little by little lost their sharp outlines and changed into osmotic balls

Fig. 6

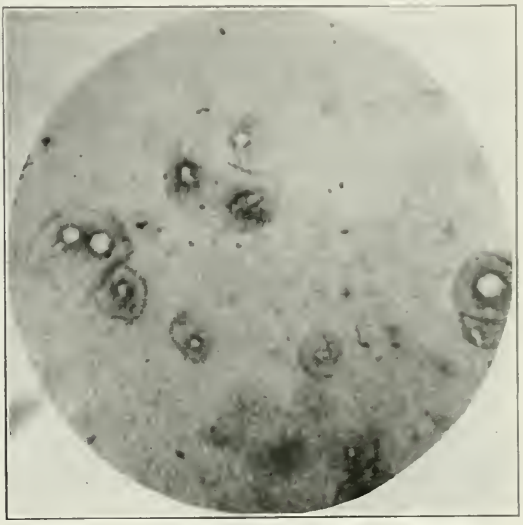

Fig. 7

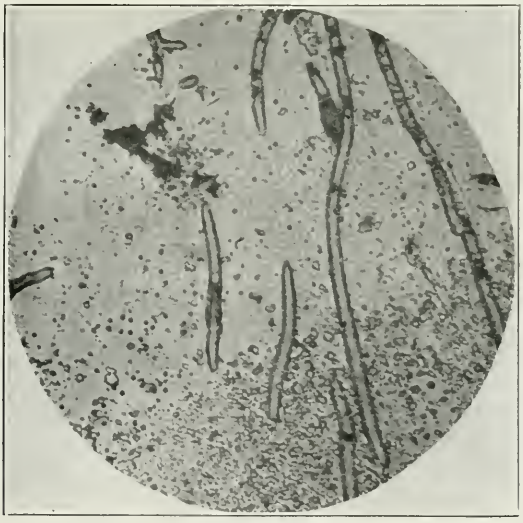

Fig. 8

looking like cells and amebæ which moved about slowly. These structures could be washed, stained and preserved in Canada balsam.[3]

In 1918 I observed that better results were obtained when the two solutions were allowed to diffuse into each other through a thin porous wall. If a Chamberland filter or an ordinary unglazed porous cup is filled with a solution of

potassium silico-carbonate and this is then immersed in a beaker containing one per cent calcium chloride (Fig. 1) there appear, by the next day, upon the surface of the porous cup, numerous tubules which, when observed microscopically, are seen to consist of beautiful hexagonal cells (Fig. 2) often showing nuclei (Figs. 3, 4, and 5) and sometimes figures resembling karyokinesis (Fig. 6).

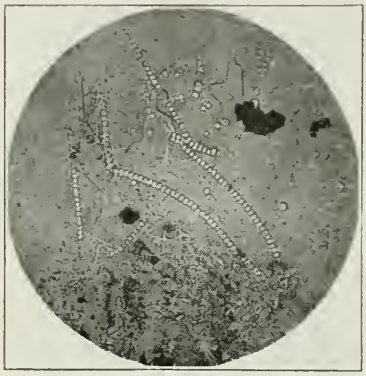

Fig. 9

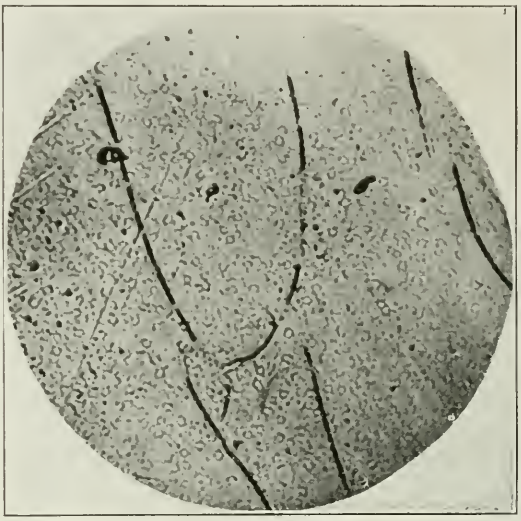

Fig. 10

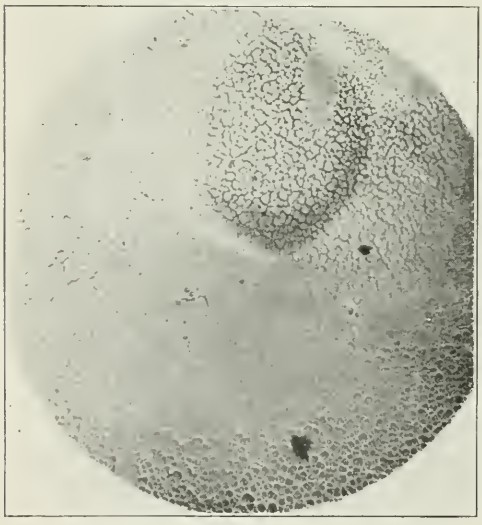

Fig. 11

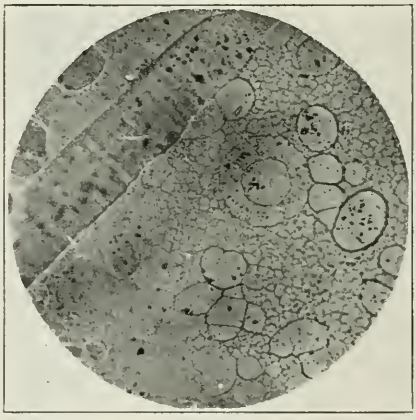

Fig. 12

I have sent many such preparations to my colleagues abroad for their personal study. Cells thus produced resemble very closely those of nature.

Cellular structures thus produced are easily destroyed by acids. To avoid this I have made silicate figures by employing another double salt, namely, that of the silico-fluorides. For this purpose I merely expose an ordinary glass slide to the vapors emanating from a bottle filled with hydrofluoric acid.

After the vapors have acted upon the glass for two or three days the slide is washed and stained with Kühne's blue. The microscope reveals numerous structures looking like isolated cells (Fig. 7), lower organisms (Fig. 8), spores and streptococcal chains (Fig. 9), bacteria (Fig. 10), and the micellar structures of protoplasm (Figs. 11 and 12), all produced in consequence of the formation of insoluble colloid silico-fluorides, and more or less hardened by an excess of hydrofluoric acid. The best structures are produced at a distance from the point where the vapors attack the glass most intensely.

I hold that these studies on the structures exhibited by colloid silicates are not without biological significance. Quite apart from the fact that the production of such structures and their identity with the morphology of living protoplasm indicates that the *physical* basis underlying the two must have much in common. I believe also that a parallelism exists from a *chemical* point of view. Has living protoplasm also an inorganic skeleton upon which is superimposed a "body and flesh" of such organic materials as the albumins? I incline to a positive answer in this matter because, on the one hand, the silicon compounds are widely distributed throughout the living world (a point to which I have repeatedly called attention in years past), while, on the other, the opinion that living matter consists exclusively of albumins can hardly be said to have been proved. The albumin theory may be true, but it is a significant fact that artificial cells mimicking in their morphology the living have not thus far been produced from albumin. They may, of course, be produced in the future in which case support will be given to Pflüger's theory regarding the origin of life on this planet by way of the cyanogen compounds; but until such proofs are forthcoming, a study of such inorganic cells as I have described is to be recommended.

Of the two theories, that which holds that life may have had its beginnings in inorganic materials is the easier, for albumins, fats, formalin, glycolic acid, etc., are all labile substances and hardly conceivable as existent in a primitive world. On the other hand, the interaction of solutions produced by the action of water and of atmosphere upon the earthy constituents of the soil is able to produce at once all the cellular structures which I have described.

I do not pretend to have proved through my experiments that such has been the source of living things upon this earth, but I do believe that I have at least obtained some evidence in this direction.

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TYPES OF PNEUMOCOCCUS IN LOBAR PNEUMONIA*

By Russell Richardson, M.D., Philadelphia, Pa.

PNEUMONIA has, in recent years, become one of the greatest scourges of the civilized world. There are few regions where it is not found. Especially is it prevalent where many people are moved from their native surroundings to a climate which is different from that to which they are accustomed. The reports of our health departments show such an increase that, at present, when tuberculosis is decreasing, pneumonia during several months of the year holds first place as a cause of death. Notwithstanding the importance of the disease and the large amount of work that has been done upon it we have made little if any decrease in its mortality. Our very treatment shows our helplessness in the face of the disease. We can only stand by to support the patient with our treatment while he fights his own battle. This he does by means of antibodies as we now know. However if he lacks the ability to form these in sufficient amount our supporting treatment is useless. Since the latter part of the last century attempts have been made to supply these antibodies in sufficient concentration to terminate the infection. Eyre and Washburn[1] tried for protective bodies a serum made by Dr. Pane of Naples. They used three cultures of pneumococcus from cases of pneumonia, one from a case of empyema following pneumonia, and one from the mouth of a normal individual. The serum protected in high dilution against two of the pneumonia cultures and the empyema culture, very slightly against the normal culture and not at all against the third pneumonia culture.

Neufeld[2] demonstrated as a probable explanation of such results as the above, that there were varieties of pneumococci which, though resembling each other morphologically, nevertheless showed very distinct immunologic differences. Dochez and Gillespie[3] followed this with a more detailed study dividing the strains of pneumococci into four types or groups. These they numbered I, II, III, and IV. Groups I and II were identical with the two organisms with which Neufeld had worked. They differed from each other only slightly morphologically but immunologically they were entirely distinct. These immunologic differences they demonstrated by animal protection and agglutination. Group III was the organism otherwise known as pneumococcus mucosus. It is unlike the other groups morphologically, as well as in its immune properties. Group IV was a heterogeneous group comprising all those cultures which did not belong in one of the other groups. These organisms somewhat resembled Groups I and II morphologically but did not interact immunologically either

Table I

TYPE	NUMBER OF CASES	PER CENT
I	28	45
II	12	20
III	9	14
IV	13	22

*From the Ayer Laboratory of the Pennsylvania Hospital.

with the other groups or among themselves. This classification has been the standard followed by all later work. The first 62 cases of pneumonia studied they found distributed as shown in Table I.

A continuation of this work for the following years at the Hospital of the Rockefeller Institute gave results closely approximating Table I.[4] The result of four years' examination of cases there is shown in Table II.[5]

TABLE II

TYPES	1912-13	1913-14	1914-15	1915-16	TOTAL	PER CENT
I	29	22	21	33	105	33.54
II	8	28	35	28	99	31.62
III	7	6	9	13	35	11.18
IV	16	13	17	28	74	23.64

The mortality of the different types varies greatly as shown by Cole.[6] Type III is by far the most fatal, Type II being generally considerably less so, and Type I slightly less fatal than Type II. Type IV is not nearly so severe an infection and has a correspondingly low mortality. The mortality of 103 cases as given by Cole is shown in Table III.

TABLE III

TYPE	NUMBER OF CASES	DEATHS	PER CENT
I	28	7	25
II	25	9	36
III	17	8	47
IV	33	2	6

Lister[7] working on pneumonia in South Africa has found five groups of pneumococci. Three of these groups are identical with Groups I, II, and III as found in this country, while two others, which are prevalent among the natives there, have not been found here.[8]

Mathers[9] in Chicago during the winter of 1914-15 found the distribution of types remarkably like the results at the Rockefeller Institute except that the predominating type differed. In New York Type II was found in the greater number of cases and in Chicago Type I. Table IV shows the results of this work.

TABLE IV

TYPE	NUMBER OF CASES	PER CENT	DEATHS	PER CENT
I	50	45.	13	26
II	25	22.5	7	28
III	5	4.5	4	80
IV	31	28	8	25

The mortality among these cases also bears a striking resemblance to the others. So few cases of Type III are found that the percentage of mortality varies more than the other types.

Clough[10] at the Johns Hopkins Hospital had very few Type II cases as com-

pared with other workers, and no deaths, while Type IV showed the high mortality of 57.2 per cent. The distribution of types among 54 cases is shown in Table V.

Table V

TYPE	NUMBER OF CASES	PER CENT	DEATHS	PER CENT	COMPLICATIONS	PER CENT	LEUCOCYTOSIS
I	19	35.2	7	36.8	6	31.6	24,100
II	3	5.5	0	0	1	33.3	27,300
III	8	14.8	8	100	4	50	11,800
IV	14	25.9	8	57.2	5	35.7	24,600
Atyp. II	9	16.7	4	44.4	2	22.	22,800

It will be noticed also that the Type III cases had the remarkable mortality of 100 per cent. These cases always have a high mortality, but seldom as high as in this series.

Frissell and Famulener[11] in New York found among 19 cases no Type III, and a rather large number of Type I cases. Their results are shown in Table VI.

Table VI

TYPE	NUMBER OF CASES	PER CENT	
I	9	50	1 death
II	7	38.8	4 "
III	0	0	
IV	2	11.1	1 "

In Pittsburg at the Allegheny General Hospital Hartman and Lacy,[12] examining 99 cases, found the distribution and mortality closely agreeing with earlier results. Their figures are shown in Table VII.

Table VII

TYPE	NUMBER OF CASES	PER CENT	DEATHS	PER CENT
I	41	41.4	15	36.5
II	29	29.3	10	34.5
III	6	6	4	66.6
IV	23	23.2	6	26

Notwithstanding the difficulty of obtaining satisfactory specimens for examination from children, a considerable number of these cases have been investigated.[13, 14, 15, 16] The results of these examinations point to an increased percentage of Type IV cases with a higher mortality in this type.

During the stay of the troops on the Mexican border Nichols,[17] investigating the pneumonia epidemic there, found a high percentage of typical types, especially Types I and II. Some of his cases were treated, probably thus accounting for the low mortality in Type I. His results are given in Table VIII.

Table VIII

TYPE	NUMBER OF CASES	PER CENT	MORTALITY, PER CENT
I	84	56	14.8
II	33	22	30.0
III	3	2	33.0
IV	30	20	13.3

During the past year type determinations have been carried on at the various army cantonments. McClelland[18] at Camp Beauregard found the distribution and mortality as follows:

TABLE IX

			MORTALITY	
TYPE	NUMBER OF CASES	PER CENT	NUMBER OF CASES	PER CENT
I	33	29.2	4 (serum used)	12.1
II	11	9.7	1	9.1
III	5	4.4	1	20.0
IV	64	56.7	6	9.4

The work at Camp Funston, Kansas, gave results in 135 cases similar to those of McClelland except that the Type II cases made up a slightly larger percentage of the total.[19] Dick[20] at Camp Pike found that 48 per cent of 60 cases examined showed pneumococci, and of these there were 21 per cent Type I, 34 per cent Type II, and 45 per cent Type IV. Only one case of Type III was observed.

In the present work type determinations were made in 413 cases of lobar pneumonia during the winters from 1913 to 1917. Only cases between October 1 and May 1 are included. During the second, third and fourth winters serum was used in the treatment of Type I and part of Type II cases, after the method used by Cole at the Rockefeller Hospital, and so the mortality for these two types is given for only the first year.

The determinations were made on the basis of agglutination together with cultural and morphologic characteristics. A 24-hour broth culture was used with an equal amount of immune serum, obtained from the Hospital of the Rockefeller Institute. At first the serum was used undiluted but later in dilutions of 1:10. This was done with both Type I and Type II sera, controls being used in each case. If the strain in question did not agglutinate with either serum, the differentiation between Groups III and IV was then made on the basis of morphology and growth, which are very distinctive. When a rapid differentiation was wanted the following method was used: There was injected into the peritoneal cavity of one or two white mice from one-half to one c.c. of sputum rubbed up with normal saline solution. After two to four hours, if a peritoneal puncture showed many organisms, the mouse was killed and an agglutination test made, using a suspension of the peritoneal fluid. Some of the fluid was inoculated into broth and incubated for two hours and another agglutination test made on this culture. A precipitin test was also done in most cases. At the same time a culture was made from the heart blood and an agglutination reaction done later on this to control the first reaction. Especial care was taken to rule out any strains of streptococci which are the organisms in so many cases of pneumonia.

During the season of 1913-14, determination of types was made on 115 cases. These were distributed among the types as shown in Table X. The mortality is also shown.

Table X

TYPE	NUMBER OF CASES	PER CENT	DEATHS	PER CENT
I	39	33.9	12	30
II	28	24.3	7	25
III	6	5.2	3	50
IV	40	34.7	5	12

During the winters of 1914 to 1917 there were 308 examinations made. These are given in Table XI.

Table XI

TYPE	1914-15		1915-16		1916-17	
I	27	31.3%	17	20.7%	34	26.3%
II	12	13.9%	21	25.6%	26	20.1%
III	7	8.1%	10	12.0%	11	8.5%
IV	40	46.5%	33	41.4%	58	44.9%
Totals	86		81		129	

The normal mortality of Groups I and II it is not possible to estimate, because of the use of serum in these cases. The mortality of Groups III and IV was as follows:

Table XII

TYPE	1914-15	1915-16	1916-17
III	3 43%	4 40 %	5 45.4%
IV	8 20%	6 17.6%	13 19.1%

Five cases presented a combination of two types. Two cases had Types I and III, both of which died. Two cases had Types II and III combined and one had Types I and IV. All of these recovered. It will be noticed in comparing these tables that, both in distribution and mortality, there is more or less agreement, within limits, between epidemics of different years. The scattering pneumonias of the summer season, which have not been included in this series, are generally in our experience Type IV cases.

In order to find out what differences there might be in the infections caused by organisms of these groups, a study was made of the typical symptoms of the disease and some of its complications. The symptoms chosen were cough, pain in chest, dyspnea and chill. These with the leucocytosis make up so large a part of the early picture of pneumonia. Table XIII shows the percentage of cases of each type in which these symptoms were present.

Table XIII

TYPE	COUGH	PAIN	DYSPNEA		CHILL
I	88%	81%	74%	severe 46% mild 28%	73%
II	90%	87%	70%		67%
III	75%	75%	75%		62%
IV	81%	91%	57%	severe 15% mild 42%	87%

As will be seen, the percentage of cases showing cough and pain does not vary noticeably in the four groups. On the other hand, with regard to dyspnea and chill, there is a considerable difference. The so-called typical groups, i. e., I, II, and III, show a higher percentage of dyspnea and a lower percentage of chill than do the heterogeneous. The term "chill" was not used in regard to chilly sensations, but only to a distinct shaking chill. The number of cases of type III are so few that it is not possible to place much importance on the figures for that group.

The average leucocytosis, on the other hand, shows a marked similarity in all four groups:

Table XIV

TYPE	LEUCOCYTES
I	20,900
II	16,700
III	21,800
IV	18,000

Of the complications of pneumonia there were studied meningitis, pulmonary tuberculosis, delayed resolution, lung abscess, empyema and endocarditis. In Table XIV are shown the number of cases of each which occurred in the various groups. Only cases of the first year, when serum was not used, are given.

Table XV

TYPE	MENINGITIS	PULMON. TUB.	DELAYED RESOLUTION	LUNG ABSCESS	EMPYEMA	ENDOCARDITIS	TOTAL
I	–	4	–	1	1	1	7
II	–	–	–	2	–	–	2
III	1	1	–	–	–	–	2
IV	1	2	3	–	6	1	13

Perhaps the most interesting point in regard to the distribution of the complications is that about twice as many were found in the Type IV cases as in any other group. One case of pneumococcus meningitis caused by a Type I organism came to the hospital. A history of preceding pneumonia was not obtained. The tuberculosis became evident on the clearing up of the pneumonia, though in how many cases it had been there before it is not possible to say.

On questioning the patients regarding what they considered to be the cause of their pneumonia, it was found that a large number of those with Type IV infection were able to remember a distinct occurrence to which they attributed their illness. Such exposures as sitting in a draft when warm, an engineer coming out from the hot engine room on a cold night, a man going outdoors after being in a warm swimming tank, etc., were a common history. Type IV organisms are commonly present in the mouth forming a constant source of infection in cases such as these. Lyall,[21] examining tuberculosis patients, found that when pneumococci were present in the mouth very few were other than Type IV. Studies in this laboratory on normal individuals and on those with slight coryza show

that Type IV is apparently predominant in number. Dochez and Avery[22] have shown that the typical types usually disappear from the mouths of convalescent pneumonia patients in from 12 to 90 days, leaving only Type IV, if any, present.

On the other hand, those patients with infection of the typical types became ill without any apparent cause. The onset was that of a true epidemic infection, without any noticeable loss of resistance preceding. Nichols,[23] working on pneumonia in the army, where on account of age and physical condition, diminished resistance should not be a large factor, found 78 per cent of cases caused by typical types. It would seem then that the infections caused by the typical and atypical types may differ more or less. The latter, being less virulent, may need in most cases a loss of individual resistance for its development, while the former are more truly an epidemic infection, though the lessening of resistance may be a factor in these cases also. The greater number of complications in cases infected with a less virulent organism also lead toward this conclusion.

The unfailing regularity with which the same type of organism is found in several specimens of sputum from the same case of pneumonia, and the specificity of the agglutinations are of great importance in the practical application of this work to the serum treatment of pneumonia. The number of cases in which the type has been determined, widespread as they are, show that at least one-fourth of all cases are Type I which is now amenable to serum treatment, and that from one-half to three-fourths are caused by the typical types for which we may hope to have a satisfactory serum later.

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LABORATORY METHODS

A SIMPLE METHOD FOR THE PREPARATION OF A SPINAL ANIMAL*

By Hugh McGuigan, M.D., and W. J. R. Heinekamp, B.S.,
Chicago, Ill.

IN the preparation of spinal animals to study the function of the central nervous system and to analyze drug action on this system various complicated operative procedures have been advanced.

In Sherrington's spinal animal the head is removed. Jackson (Experimental Pharmacology, 1917, p. 195 et seq.) after a major operation injects chloroform into the vertebral artery and in this way destroys the brain. The chloroform is prevented from returning to the heart by compression of the return venous circulation. This method is not always successful, and the heart is frequently injured by the chloroform. Luckhardt (quoted by Jackson) has succeeded in destroying the brain by injections of chloroform into the carotid ar-

Fig. 1

tery. This method is somewhat less involved than injection into the vertebral artery, but has many of its disadvantages. Other workers have destroyed the brain by injecting a 3 per cent suspension of starch granules. In all these methods the blood pressure in the spinal dog, according to Jackson, is about one inch above the base line. From our point of view these methods are now of historical interest only, and show the usual steps in research—that is—from complicated to simpler and better methods.

*From the Laboratory of Pharmacology, University of Illinois, College of Medicine.

In the investigation of strychnine action by one of us (McGuigan, et al.: Journal of Pharmacology and Experimental Therapeutics, ii, p. 319; v, p. 469, and viii, p. 43) a similar advance from the complicated to the simple is recorded. In these latter investigations we finally injected drugs directly into the fourth ventricle, and into the spinal canal in other regions. In the preparation of spinal animals this method may also be used. One or two c.c. of chloroform (other drugs may be used) injected into the fourth ventricle is all that is necessary. The animal prepared in this way is far superior for work than one by the older methods of preparation.

METHOD

Anesthetize the animal and insert a tracheal cannula for artificial respiration. If in the experiment blood pressure tracings are desired these may be taken care of in the usual way. Then when the spinal condition is desired, bend the animal's head sharply on its chest and insert a medium-sized hypodermic needle between the occiput and atlas on the median line and press it into the ventricle (Fig. 1). There may be some slight difficulty in getting through, since in some animals there is an overlapping of the bones. However, if one keeps in the midline, the difficulty is very slight and once a puncture has been made a repetition is very easy. The needle usually drops through the resistance in the last step and an abundance of clear fluid is a striking indicator of the location. Frequently one strikes the respiratory center; with a little practice this can be avoided if desired. In the preparation of the spinal animal injury of the respiratory center is of no special moment.

ADVANTAGES OF THE METHOD

It is simple, bloodless, efficient, and has practically no effect on the blood pressure. Absorption from the ventricle is apparently slight, so that there is no direct action on other organs.

SEDIMENTING SUSPENSION OF LIVE BACTERIA ON A LARGE SCALE*

E. M. Houghton, M.D., and N. S. Ferry, M.D., Detroit, Mich.

IN the sedimentation of bacterial suspensions or broth cultures for the preparation of bacterial vaccines, or for the purpose of clarifying the broth before filtration in the process of obtaining toxins, where the question of time as well as quantity must be considered, laboratories have been compelled to resort to the use of a centrifugal machine run on the principle of a milk separator, such as the Sharples machine, which will permit of a continuous flow of liquid to and from the machine.

It has been found, however, that when the bacteria are being sedimented in a live state, it is rather an unsafe procedure for the operator unless some pro-

*From the Research Department, Parke, Davis & Company, Detroit, Mich.

tection is afforded against the fine spray, containing bacteria, which is given off from the liquid as it leaves the rapidly revolving bowl.

It has also been observed that the chances of obtaining a sediment or a filtrate in an uncontaminated state are rather doubtful unless the entire mechanism can be thoroughly sterilized before and after operation.

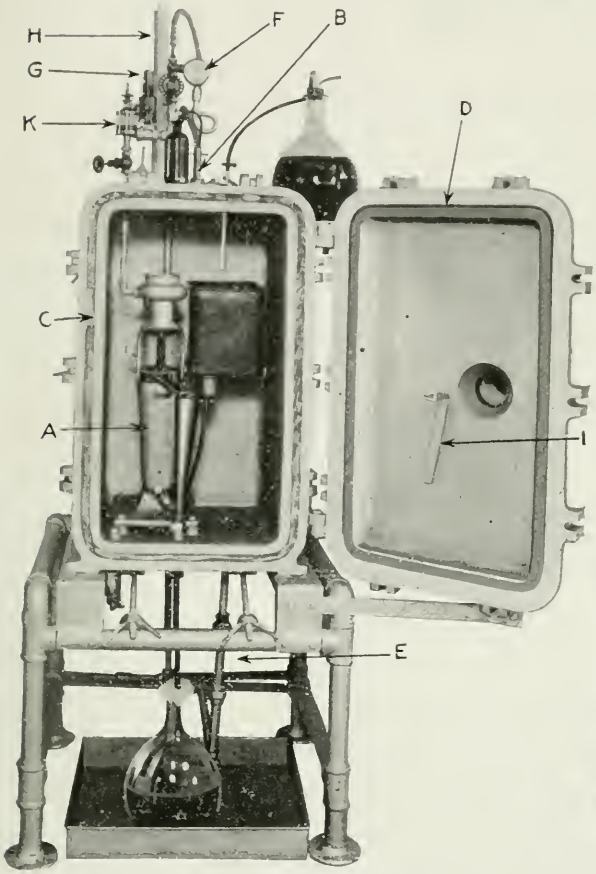

Fig. 1

A. Centrifuge.
B. Atomizer.
C. Cotton gasket
D. Rubber gasket.
E. Pipe to vacuum system.
F. Air pressure gauge.
G. Air safety valve.
H. Discharge pipe to centrifuge.
I. Handle to supply can.
K. Oiler to centrifuge.

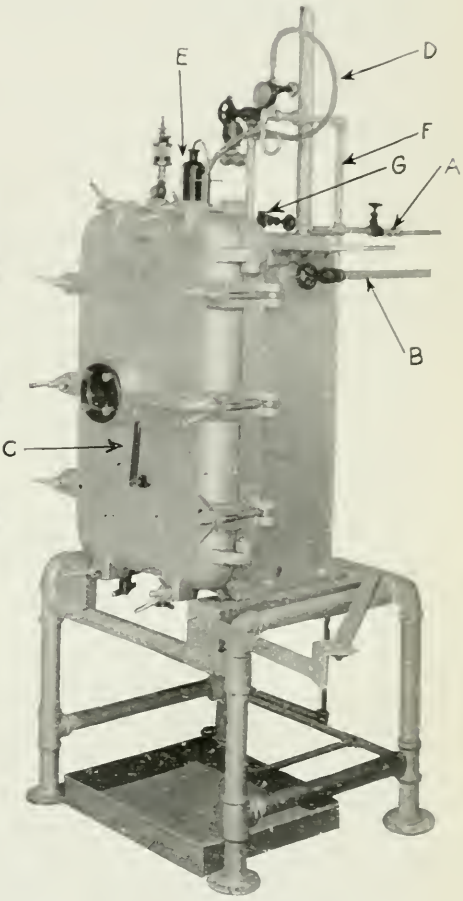

Fig. 2

A. Pipe to steam gauge.
B. Steam pipe.
C. Handle to supply can.
D. Air pipe to atomizer.
E. Bottle of germicide for atomizer.
F. Compressed air pipe.
G. Valve for siphon intake.

In order to obtain conditions as safe as possible for those in close proximity to the machine, and maintain, at the same time, an aseptic operation throughout, an apparatus has been devised according to plans suggested by one of us (E.M. H.) which fulfills the necessary requirements without influencing in any way the efficiency of the separator.

The apparatus in question consists of a cast iron jacket, opening on the

front, with a swing door, which completely encloses a Sharples turbine-driven laboratory centrifuge, including its supply can. The jacket is so constructed that it becomes an autoclave, when the door is securely shut, and the valves of the various pipes leading to the jacket are closed, in which the entire mechanism of the centrifuge can be sterilized with live steam at a temperature of 120°C. for any length of time deemed necessary. At the same time connection is maintained between the jacket and a vacuum system in order to facilitate the drying of the several parts of the machine, after the steam has been exhausted, without opening the door of the jacket.

To further insure the safety of the operator, in addition to a rubber gasket, on the inner surface of the door where it comes in contact with the rim of the jacket, is found a roll of cotton, soaked in a germicide, packed in a groove surrounding the frame of the door, making the door crack entirely germ-proof.

The apparatus is also equipped with a safety valve for the compressed air system as well as an automatic steam pressure gauge to doubly safeguard both the operator and the machine.

If it is found necessary to gain access to the machine any time before the parts can be autoclaved, sterilization of all exposed surfaces may be accomplished by means of a large atomizer, connected with the compressed air pipe and a bottle of some strong germicide, which is placed in the top of the jacket. This atomizer is so constructed that it will revolve at an angle of 360° in order to reach all sides and corners, and of such dimensions that it is capable of discharging with an air pressure from 30-50 pounds, causing the entire chamber to be filled with a fine cloud or spray and rendering any exposed parts perfectly safe to handle within a short space of time.

In order to control the flow of liquid from the supply can to the bowl, when the door is closed, a lever, having a handle on the outside of the door is made to connect with the faucet of the supply can so that it can be manipulated at will without exposing the inside of the jacket.

The apparatus has been given a thorough trial for several months on various vaccines and toxins, and has been found perfectly efficient as to its qualifications as a sterilizer, as well as a separator.

In centrifugalizing a certain lot of material the procedure is a follows: set up the machine for operation, clamp the door, shut all necessary valves, autoclave and then dry with vacuum. Start machine, allow suspension to siphon from flask, on top of jacket, into supply can. From there it will flow into the bowl and thence out of the nozzle through the funnel into the plugged flask under the jacket. The sediment will be found in the bowl and the clear filtrate in the flask, both uncontaminated.

AN APPARATUS FOR THE QUANTITATIVE DETERMINATION OF UROBILIN AND UROBILINOGEN*

By J. D. Boyd, B.Sc., Iowa City, Iowa

THE apparatus herewith described has been found convenient in making quantitative determinations of urobilin and urobilinogen. It has been in use for nearly a year.

It was constructed from a Hellige colorimeter and a hand spectroscope, and consists essentially of a hollow glass wedge which can be moved vertically before a fixed spectroscope. If the Hellige colorimeter is not obtainable, a similar apparatus can be made without much trouble.

The wedge is made by cutting pieces of clear glass to the desired size, and then grinding the edges with carborundum powder and water on a sheet of plate glass until the surfaces to be united approximate closely at the desired angle. (See diagram for dimensions.) The pieces are cemented together with Canada balsam; after the cement is partly set, the cell should be baked at approximately

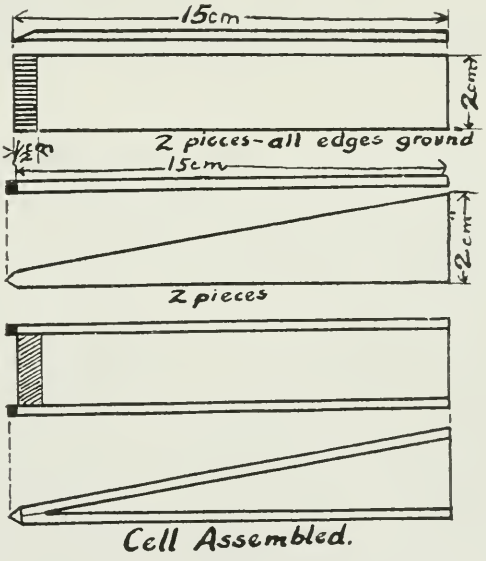

Fig. 1

120° C. for two or three days. To prevent the cement from being dissolved out, a little melted paraffin should be run down the seams, but should not be allowed to come in contact with the anterior or posterior surfaces of the wedge.

For those unfamiliar with the Hellige colorimeter the following short description may suffice.

The cell is supported on the distal panel of the colorimeter, which is provided with a pane of milk glass somewhat larger than the cell. This panel is movable up or down by means of a rachet, and is provided with a scale of the same length

*From the Chemical Laboratory of the Department of Internal Medicine, State University of Iowa, Iowa City.

as the depth of the cell, and graduated in hundredths. The spectroscope is attached to the fixed panel parallel to this by means of a U-shaped brass block provided with lugs.

The whole device is mounted against a board provided with a one-inch hole,

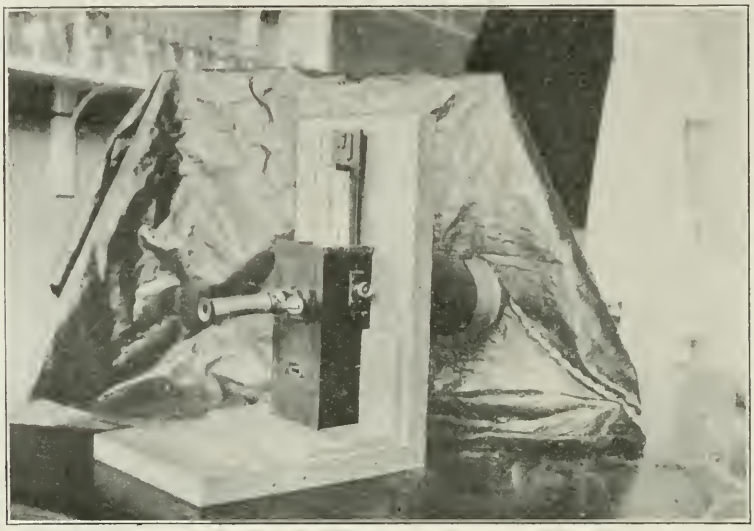

Fig. 2

Fig. 3

placed opposite the spectroscope, through which enters the light from a 40-watt electric lamp fixed to the back of the board. The lamp is enclosed in a tin cylinder. The apparatus is best used in a dark room.

PROCEDURE

The sample is prepared for examination according to the method of Wilbur and Addis. The cell which holds about 10 c.c. is filled with the solution, and the

point is found where the spectrum just disappears with moderate light, but reappears when the light is diminished by changing the light screen of the spectroscope. We prefer to examine for urobilin before adding the Ehrlich's reagent, but after acidification. The band is more sharp under these conditions. The cell used here is 1 cm. broad at the part corresponding to 100 on the scale.

CALCULATIONS

If the scale-reading be represented by R, then $\frac{100}{R}$ represents the number of times the sample can be diluted and the spectrum be just visible with the scale at 100. This value, multiplied by the previous dilution will give the total dilution value.

A SIMPLIFIED TECHNIC OF APPLYING THE ELECTRODES IN ELECTROCARDIOGRAPHY*

By David Felberbaum, M.D., New York City

THE usual method of applying the German silver plate electrodes upon the limbs of the subject in taking electrocardiographic records is more or less time consuming and untidy. This procedure is carried out by wrapping flannel bandages that have been soaked in warm saline solution about the limbs, enclosing the electrodes. These bandages soon become soiled and the drippings rapidly cover the surroundings of the patient. We have frequently found that when a number of consecutive electrocardiographic examinations are made, static interferences become very annoying, due to the crustations of salt, making conductors out of the chairs, etc.

To overcome these drawbacks I developed the following simple technic.

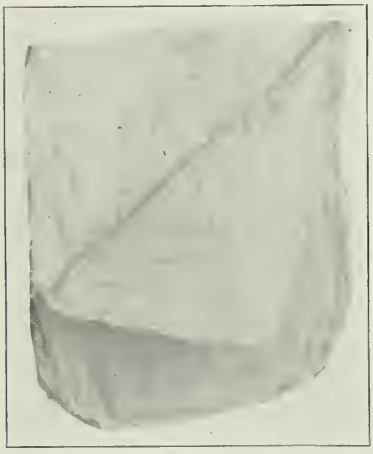

Fig. 1.—This illustrates the bag with the single layer turned back, showing how the bag is constructed.

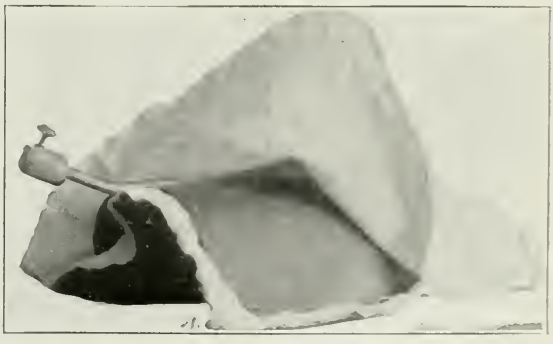

Fig. 2.—This illustrates the bag with the electrode placed between the two layers.

*Cardiological Department Montefiore Home and Hospital, N. Y.

A sort of bag, or better, mittenlike sack is made of heavy double-nap flannel. This is cut to correspond with the shape of the electrodes, but considerably larger. Four layers are sewed together to form the front, while a single layer forms the back of the sack. The single layer is sewed along the edge to the four layers for about two-thirds of its circumference (Fig. 1). The electrode is placed between the two after the bag has been thoroughly soaked in hot saline solution. The whole arrangement is then firmly bandaged down upon the limb of the subject by means of a wide rubber bandage. These bandages are about five inches wide and about 36 inches long, and are cut from the heaviest bandage gum supplied by the Hodgman Rubber Co., New York. The rubber bandage, besides holding this apparatus firmly to the limb, acts as an insulator, prevents the dripping, and keeps the bag warm. The rubber bandage is prevented from unrolling by placing an ordinary heavy rubber band around the end.

This arrangement is rapidly applied. Many sets of bags can be made so that each patient may be supplied with a clean one. They are neat, clean, portable, occupy very little space, and may be washed or even sterilized.

It has been repeatedly demonstrated that this arrangement causes less resistance in the string circuit than the former method. The resistance varies from a few hundred to two or three thousand ohms. I seldom need to employ the ten millivolt switch, and in that way always work with a highly sensitive string.

In conclusion, this method affords us a simple, rapid, portable, clean, and accurate means of attaching the electrode. The electrodes are kept free from corrosions and the resistance of the string circuit is kept at a minimum.

A SIMPLE METHOD FOR DETERMINING THE CAPACITY OF "TO CONTAIN" PIPETTES*

By Mary W. Wheeler, B.S., Albany, N. Y.

THE inability to procure accurately standardized "to contain" pipettes recently, made it necessary to grind down the slightly broken tips of some that had been in use, and then to restandardize these. Since it is necessary to determine the total volume of liquid in a "to contain" pipette and not the volume delivered from it, the usual method given in text books for standardizing "to deliver" pipettes is not applicable. However, this method requires but few modifications. The details of the method as modified are as follows:

1. A ground-glass-stoppered bottle filled with distilled water and a small covered dish (an ordinary stender dish) containing a piece of filter paper are weighed together on accurate analytical balances.

2. By means of a suction apparatus as shown in the accompanying diagram, water is drawn into the pipette from the bottle just to the graduation mark. Any water adhering to the outside of the pipette is then wiped off with the weighed

*From the Division of Laboratories and Research, of the New York State Department of Health, Albany, New York.

filter paper, which is then immediately returned to the dish and covered to prevent evaporation of moisture.

3. The bottle and dish are reweighed and the weight of the water contained in the pipette determined by difference.

4. The temperature of the water is determined just before or after filling the pipette. If the temperature of the room is practically constant, this is most easily done by finding the temperature of water in a breaker or bottle (similar to the one in use) standing near the apparatus and subjected to the same condition.

5. Five determinations are made for each pipette, the pipette being thoroughly dried between each determination by rinsing several times with alcohol and finally with ether.

6. From Tables 35 - 47 "Standard Density and Volumetric Tables," U. S. Bureau of Standards, Circular No. 19, correction for variation in temperature is made, the volume of the pipette being corrected to 20° C.

To check the accuracy of this method, the capacity of six German certified 2 c.c. "to contain" pipettes was determined.

The determinations made on one of these pipettes is given below in detail.

Pipette No. 2720. Two c.c. "to contain," certified as +.001 c.c. Temperature of Standardization 20° C.

(a) Weight of bottle of water, filter paper, and stender dish
(b) Weight of bottle of residual water and stender dish with filter paper
(c) Weight of water contained in pipette as determined by difference

(1)	(4)
(a) 95.6485 gm.	(a) 93.1110 gm.
(b) 93.6526 "	(b) 91.1149 "
(c) 1.9959 "	(c) 1.9961 "
(2)	**(5)**
(a) 91.7726 gm.	(a) 91.1149 gm.
(b) 89.7772 "	(b) 89.1195 "
(c) 1.9954 "	(c) 1.9954 "
(3)	
(a) 95.1068 gm.	
(b) 93.1110 "	Average weight of water contained in pipette, 1.99572 gm.
(c) 1.9958 "	

Temperature correction from Table No. 36, U. S. Bureau Standards, Circular No. 19.
Amount to be added to weight of water in grams as determined to obtain actual capacity of pipette in cubic centimeters at 20° C. = .00529.

1.99572 gm. weight of water in pipette
.00529 correction

2.00101 c.c. actual capacity at 20° C.
2.00000

+.00101 c.c. capacity error

The following table gives the results of the determinations of the six pipettes.

Capacity Error of 2 c.c. "To Contain" Pipettes

No. of pipette	Capacity error as certified	Capacity error by above method*
2710	— .002 c.c.	— .00215 c.c.
2712	— .003 c.c.	— .00331 c.c.
2717	+ .002 c.c.	+ .00224 c.c.
2720	+ .001 c.c.	+ .00101 c.c.
2726	+ .002 c.c.	+ .00228 c.c.
2729	+ .003 c.c.	+ .00312 c.c.

In order to determine the error which would be introduced by not wiping off any water adhering to the outside of the tip of the pipette, the capacity of pipette No. 2720 was again determined. The method was the same as before

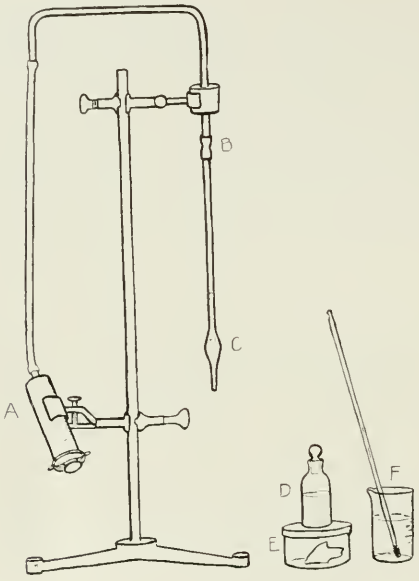

Fig. 1.—Apparatus for standardizing "to contain" pipettes. *A*, 5 c.c. syringe draw; *B*, rubber connection for holding pipette; *C*, "to contain" pipette to be standardized; *D*, ground-glass stoppered bottle containing water; *E*, stender dish containing filter paper; *F*, beaker of water containing thermometer, for temperature control.

except that the tip was not wiped with the filter paper. Only three determinations were made this time as the error was so apparent. The result was as follows:

Pipette No. 2720. Two c.c. "to contain," certified as +.001 c.c. Temperature of Standardization 20° C.

(a) Weight of bottle of water
(b) Weight of bottle of residual water
(c) Weight of water contained in pipette as determined by difference

(1)		(3)	
(a)	36.7190 gm.	(a)	32.7226 gm.
(b)	34.7221 "	(b)	30.7261 "
(c)	+1.9969 "	(c)	1.9965 "

(2)	
(a)	34.7221 gm.
(b)	32.7226 "
(c)	1.9995 "

Average weight of water contained in pipette, 1.99763 gm.

*The pipettes are certified to the third decimal place only. The last two figures in this column are added to show that a slight variation here would not alter the final result of the determination.

Temperature correction from Table No. 36, U. S. Bureau of Standards, Circular No. 19.
Amount to be added to weight of water in grams as determined to obtain actual capacity of pipette in cubic centimeters at 20° C.=.00564.
C.=.00564.

1.99763 gm. weight of water in pipette
.00564 correction

2.00327 c.c. actual capacity at 20° C.
2.00000

+.00327 c.c. capacity error

CONCLUSIONS

The method as given above for determining the capacity of "to contain" pipettes is simple, practical, and sufficiently accurate for laboratory use.

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ON THE DETECTION OF CHLORETONE IN MOTHER'S MILK*

By J. E. Blanner, Detroit, Michigan

IT IS a widely recognized fact that milk from lactating mothers may possess a foreign taste, odor or color following the ingestion of certain substances. As concrete examples, alcohol has been found,[1] likewise opium and morphine, zinc, iron, lead, arsenic, antimony, bismuth and mercury. These facts become of utmost importance in reference to the administration to the mother of such drugs as may be injurious to the child.

The extensive use of chloretone therapeutically calls for further research in this particular on this important drug. The presence of chloretone in the tissues, organs and fluids of the body after ingestion, has been conclusively demonstrated by Aldrich.[2]

The purpose of these experiments has been to determine the presence and amount, if any, of chloretone in the milk of lactating mothers. Humans and dogs were used as experimental subjects.

The method of demonstrating and estimating the presence and quantity of the drug was precisely that originated by Aldrich.[3] The efficacy of this method depends upon the characteristic crystalline form of chloretone, volatility with steam, and low solubility in water. A brief resume of the method may not be out of place.

The material under investigation, properly comminuted or digested if necessary, is subjected to steam distillation. Great care should be exercised in keep-

*From the Research Laboratories of Parke, Davis & Company.
My thanks are due to Sister Olimpia and Miss Peltier of the Providence Hospital, Detroit, who so kindly cooperated with me in the matter of securing patients and rendering other valued assistance.

ing all connections absolutely tight. The distillate is placed in a flask, which is connected with an upright condenser having a circulation of very cold water, and gently heated. If the test is positive, crystals of chloretone, long and feathery, will appear in the vicinity of the steam crest. A hand glass facilitates the detection in case of very small quantities. This test possesses much delicacy, as little as 1 mg. or 1 66 gr. having been readily detected.

EXPERIMENTAL

Case I.—Mrs. J. Ten gr. of chloretone were administered and after one hour 60 mils of milk were taken. Results negative.

Case II.—Mrs. A. One hour after the administration of 15 gr. of drug, 90 mils of milk were taken. Results negative.

Case III.—Mrs. S. One hour after the administration of twenty gr. of drug 60 mils of milk were obtained. Results negative.

Case IV.—Mrs. E. Two hours after administration of 10 gr. of chloretone, 60 mils of milk were taken. Results negative.

Case V.—Mrs. McM. Two hours after administration of 15 gr. of drug, 75 mils of milk were obtained. Negative results.

Case VI.—Mrs. H. Two hours after administration of 20 gr. of drug, 50 mils of milk were taken. Negative results.

Case VII.—Mrs. B. Ten gr. of chloretone administered and 60 mils of milk taken three hours later. Results negative. Four hours from time of administration of drug, 30 mils were obtained. Negative results. Five hours later 40 mils. Negative results.

Case VIII.—Mrs. C. Twenty gr. chloretone administered and samples averaging 40 mils taken at the end of every hour until five were obtained. Results proved negative.

Case IX.—Mrs. D. Ten gr. of chloretone administered and one hour later 70 mils of milk obtained. Two hours from time of first administration 10 gr. more were given and one hour later 50 mils milk obtained. Two hours from time of second administration 10 gr. more were administered. One hour later 45 mils milk obtained. Two hours from third administration 10 gr. more were administered and 40 mils milk obtained. A total of 40 gr. chloretone had been administered in a space of eight hours. No positive test obtained.

Case X.—Mrs. De T. Exact duplicate of Case IX. Negative results.

Case XI.—Mrs. R. Fifteen gr. chloretone administered and one hour later 65 mils of milk removed. Two hours from time of first administration 15 gr. more were administered and one hour later 50 mils milk obtained. Two hours later 15 gr. more drug given and one hour later 40 mils milk obtained. A total of 45 gr. of drug given in a space of six hours all produced negative results.

The above mothers were normal women in every respect and were nursing their own infants throughout the period of experimentation. No effect on the infants was discernible; however, this would be very difficult as a normal infant sleeps the greater part of the day.

The following experiments were then performed on lactating dogs.

Case A.—Lactating dog weighing 10.5 kilos was obtained seven weeks after parturition. The young were taken away at beginning of experiment. Dog normal in every respect except very thin.

Three grams of chloretone were dissolved in 3 mils of 95 per cent alcohol and poured into 60 mils of tepid water.

This suspension was administered per mouth to dog fifteen minutes after complete removal of milk by young. Dog immediately passed into profound sleep and remained in such condition for four days. At no time before recovery or after could any milk be obtained.

These results pointed to the necessity of a change in method of administration of drug.

Case B.—Lactating dog, 10.5 kilos in weight, five weeks after parturition was taken from her young and milk completely removed by mechanical suction 15 minutes before ad-

ministration of chloretone. The drug 0.5 gm. was dissolved in the least possible amount of alcohol and intimately mixed with a portion of chopped meat. Seven hours later 15 mils of milk were removed and .8 gm. of the drug were administered in precisely the same manner as before.

This portion of milk to be known as Sample 1 gave negative results.

Seventeen hours later 85 mils of milk were taken and .8 gm. of drug again given. Sample 2 also gave negative results.

Twenty-four hours later milk removed from dog as completely as possible. Amount obtained 65 mils. Dog rather drowsy at this time. One gm. of drug administered. Sample 3 tested very positive. Estimated about 2 mg.

Seven hours later milk again taken from dog. Amount obtained 15 mils. At this time only .6 gm. of chloretone given as dog had become very drowsy.

Sample 4 gave positive test.

The following morning, seventeen hours later 30 mils of milk were obtained and 1 gm. of drug again administered. Positive test for Sample 5.

Seven hours later attempt was made to obtain more milk, but only about 2 mils were obtained. Administration of chloretone omitted this time. Stimulation, only, kept dog awake. Except for great sleepiness dog is normal.

The following morning milk was again removed. Seven mils were obtained. Chloretone 1 gm. again administered.

Sample 5, while positive, but barely perceptible, undoubtedly due to small amount of milk.

No drug was given in afternoon, neither was it possible to obtain any milk.

Seventeen hours later no milk could be obtained. Necessarily all experimentation came to an end.

The question here arises as to the effect of chloretone as an antigalactagogue. The results of the experiments on dogs point to such an effect, and this is in accordance with other findings in regard to chloretone as an inhibitor of the formation of bodily fluids. No such effect, however, was noticed in the case of human subjects. This undoubtedly is due to the small amount of the drug used, as weight for weight, the dog received *in toto*, twelve times as much chloretone as any human subject.

CONCLUSIONS

Chloretone is found in the milk only upon continuous administration of very large doses.

Upon the administration of 5 to 20 gr., the usual therapeutic dose, no trace is found even though administered several times in succession.

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EDITORIALS

The Michigan State Board of Health

MASSACHUSETTS was the first state in the Union to organize a State Board of Health. This was done in 1870 and the same year the State Medical Society of Michigan advocated the formation of a board in this state and a bill providing for such a board was introduced into the legislature of 1871. However, it failed to pass in that year, but was presented again at the next legislature in 1873 and passed. The legislature provided for a board of six men, eminent and interested in sanitary science, to be appointed by the Governor. The board was authorized to employ a secretary and determine his salary and the length of the service. In July, 1873, the board was organized and began to function. The secretary chosen was Dr. Henry B. Baker, who had had three years of service in the Civil War and appreciated the importance of the work which the board was to undertake. The first president of the board was Professor Robert Kedzie of the Michigan Agricultural College.

At that time the almost universal method of illumination in homes, in hotels,

in factories, in all but the larger cities, in all villages and country places, was the kerosene lamp. The tallow dip had passed away, and the general use of illuminating gas had not come in. The electric light was awaiting the developing genius of Edison, who about that time was a newsboy on the train between Detroit and Port Huron. Even in the homes of the wealthy where gas was in use, in kitchen or garret the unsafe oil lamp was still to be found. The daily newspapers carried almost constantly the headline "Another Kerosene Horror," with sickening details of some poor woman, possibly with her children, roasted like a martyr at the stake, set on fire by a lamp explosion. Cheap and inflammable benzine was sold as an illuminant under catch names such as "sunlight oil," "French burning oil," etc., with preposterous recipes to make the material nonexplosive. Packages of common salt colored with aniline were sold and guaranteed to "kill the gas." This special source of danger confronted the Michigan State Board of Health at the threshold of its duties. The oil was improperly refined, too much of the volatile matter retained in the kerosene, and no certain method of inspection was in use, the testing of the oil being too largely left to the seller. The result of the investigations of the board led to the adoption of the "Michigan oil tester," with closed cup inspection and the flashing point as line of danger. These were made the legal methods of testing and a state oil inspector was appointed to have charge of this business. After this provision, the people of the state found a safe light. The fight, however, between the venders of oil and the people went on for nearly twenty years. It was fought with great bitterness and frequent changes in the law were adopted by the legislature.

On account of the large lakes which mark its boundaries and the many beautiful inland waters, Michigan had even at that time come to be known far and wide as a desirable summer resort. The inviting cool waters tempted the old and the young, and cases of drowning were common. Drs. Kedzie and Baker, after months of experimental investigation, developed a scientific method of resuscitating the apparently drowned. This method, long known as the "Michigan method," illustrated on posters was to be found at bathing places on the shores of all our lakes, both great and small. A few years ago a distinguished English professor of physiology demonstrated in one of the university buildings at Ann Arbor what he called a new and scientific method of treating the apparently drowned. After his lecture and demonstration, he was shown the description and cuts adopted by Michigan nearly forty years before. He read the description carefully, scrutinized the illustrations, and freely affirmed that in no marked particular was his method an improvement upon the Michigan method. The posters and leaflets with illustrations of this method can be found in the annual report of the Michigan State Board of Health of the year 1874. Thousands of these leaflets have been distributed over the state, they have been several times revised, and the latest edition which deals with the treatment of the electrically shocked as well as the drowned, may be found in the report for 1897.

It is interesting to note that as early as 1878 Dr. Henry Lyster, of Detroit, and the Honorable Leroy Parker, then of Pontiac, now living in Washington, D. C., offered a plan for the examination of candidates in sanitary science. The board had in mind the improvement of the health service of the state, thinking

that calling attention to the fact that the board would examine candidates would tend to have local boards of health appoint health officers who had thus demonstrated their suitability. Again the State Board of Health of Michigan was ahead of the movement now evidenced in our universities by the creation of courses leading to the degree of Doctor of Public Health by more than forty years. It was the intention of the board that only such persons as had passed this examination would be eligible to the position of health officer. The first examination was conducted by the board, July 14, 1880, and there were two successful candidates. The reason this procedure was so short-lived was that of the lack of applicants and the failure of the public to appreciate the value of the expert. Even up to today, any village doctor who has practiced medicine for five years without demonstrating any knowledge of the prevention of disease is eligible to the highest office in sanitation within the gift of the state.

In the seventies it was common to find the walls of the houses, even of our most prominent and prosperous citizens, covered with highly colored wall paper. Dr. Kedzie studied this paper and found that it was loaded with arsenical colors. He prepared a report in a separate volume with samples of the poisonous wall papers and distributed it in November, 1874. The title of this volume was "Shadows from the Walls of Death." The book contained a hundred or more actual samples of wall paper which had been tested and proved to contain arsenic. This raised a great cry from the manufacturers of these papers and the matter finally reached hearings before a committee of Congress. However, the people were in the end victorious and no arsenical wall papers have been found on the market for many years. Slow arsenical poisoning resulted from the use of this paper. The paste by which the paper was attached to the walls contained microorganisms which, finding abundant nourishment in the paste, grew, multiplied, formed hydrogen gas, which combined with the arsenic in the paper and was diffused through the room in the most deadly form of arsenic known to science. It may be interesting to note that in the world's great war the Germans attempted to use this gas in their barbarous methods of combat with the allies.

Up to the time of the creation of the board, little or no attention was paid to the construction, warming, and ventilation of schoolhouses. In its first report (1873), a paper on this subject was presented by Dr. Kedzie. This led finally to the passage of the law compelling the submission to the board of health of the plans for heating and ventilating of state buildings.

Meteorologic observations were first begun in Michigan in 1834, but the observations were irregular, sporadic, and inefficient. In 1864, Dr. Kedzie at the Agricultural College began the systematic study of meteorologic conditions. The State Board of Health took this up and from 1870 until the establishment of the Meteorologic Service by the United States government this work was continued in Michigan. It will be seen from this that the study of meteorologic conditions was begun on a systematic plan by the State Board of Health and was probably the first continued effort ever made to forecast the weather.

In the seventies of the last century there were no trustworthy vital statistics. We had no official and satisfactory figures showing either the birth or the death rate. Both were matters of guess. Michigan rapidly developed its mortality

statistics and is now known as one of the group of "original registration" states upon which the United States government relies for its vital statistics.

There is even now in no city, in no state, any reliable set of statistics concerning the prevalence of sickness,—what is known as "morbidity statistics." At the meeting of the Michigan Board in July, 1876, Secretary Baker presented a method for compiling such statistics and was authorized to proceed with it. These statistics were collected as long as he remained secretary of the board, but later fell into desuetude. In each of the annual reports since 1876 up to the time Secretary Baker was dismissed from service there will be found a compilation of these statistics. By means of these figures Dr. Baker established curves which showed graphically that sickness from pneumonia is quantitatively related to atmospheric temperature; in other words, the colder the atmosphere, the more sickness from pneumonia.

The Michigan Legislature wisely left the question of what are the "dangerous communicable diseases" to the State Board of Health. It may be of interest to note the years in which various diseases were placed on this list. Measles, whooping cough, scarlet fever, typhoid fever, smallpox and cholera were listed in 1873; diphtheria in 1875; puerperal fever and erysipelas in 1878; typhus fever in 1879; German measles in 1886; croup and so-called typho-malarial fever in 1889; tuberculosis in 1893; yellow fever, glanders, rabies, tetanus, pneumonia, influenza and cerebrospinal meningitis in 1895. Venereal diseases did not go on the list until 1917.

The stringent law making it obligatory upon every and each householder, hotel keeper, keeper of a boarding house, or tenant and physician, to immediately give notice to the health officer of any communicable disease within their knowledge was passed in 1883. From the time of its organization, the board began to discuss methods of reaching the masses in giving information concerning the restriction of disease and the preservation of health. At the meeting of the board on April 9, 1878, President Kedzie recommended that sanitary conventions or meetings in various parts of the state be held to discuss subjects relating to sanitation. The first convention of this kind was held in Detroit, January 7 and 8, 1880. From that time, so long as Secretary Baker retained his position, such conventions were held at least twice a year in various parts of the state, and the low death rate and the prolonged life of which the state is now justly proud were largely due to this method of diffusing knowledge through the masses of the people.

Writing about these sanitary conventions in 1898, Dr. Lee of the Pennsylvania State Board of Health gives a laughable discussion of his first attempt to follow the Michigan plan. He called a sanitary convention in the city of Philadelphia, prepared a splendid program, and invited distinguished sanitarians from all over the United States to participate. When the day came, he and his invited guests occupied the stage, but the seats in front of them were empty. Dr. Lee says:

"To reduce the statement to a mathematical proposition, I would say the size of the audience at a state sanitary convention will be inversely as the square of the population of the place in which it is held."

This the Michigan State Board of Health found to be true in a general way.

In small places, the whole population turned out, while in the larger cities the attendance was small.

One of the early good works done by the Michigan State Board of Health was the investigation of those diseases in animals which are dangerous to man. Although the laws of Michigan as early as 1869 empowered the governor to appoint three commissioners, the law was inactive until the State Board of Health took up the matter. In the first law there was no appropriation with which the work could be done. In 1885, a law was passed authorizing the Governor to appoint three commissioners and a state veterinarian. In this way came into existence our highly efficient State Live Stock Sanitary Commission.

Michigan has the enviable reputation of having the lowest death rate among the states which have been in the registration area since 1900. This is largely due to the work of the Michigan State Board of Health. In the seventies, before Koch had discovered the specific cause of this disease, the State Board of Health began to teach the people of the state that tuberculosis is a transmissible and therefore a preventable disease. As has already been stated, tuberculosis was placed on the reportable list in 1893. In 1894, and at each successive legislature thereafter until it was finally accomplished, the Michigan State Board of Health urged the legislature to build a state tuberculosis sanatorium. Finally this was accomplished, and we have today not only a state sanatorium but all of our larger cities have their sanatoria and at least eight counties have provided such institutions.

It became evident to the board that while it was reaching the adults in the state, something must be done to reach the children. This led to a most beneficent law, passed by the legislature of 1895, and modified by that of 1897, which requires that there shall be taught in every public school in Michigan the modes by which the dangerous communicable diseases are spread and the best methods for their restriction and prevention. In order to make it possible to comply with this statutory requirement, the board issued and distributed a leaflet which in a short and concise manner states how the dangerous diseases are spread and how they may be restricted and prevented. The teachers in the public schools were slow to take up this duty. Most of them were incompetent, many were indifferent, and a few were positively hostile to the movement. Even now, however, it is coming to pass that every intelligent educated man and woman and child over ten years of age knows what diseases are transmissible and what procedures are necessary to prevent their spread. When asked by a Massachusetts man why tuberculosis is much less prevalent in Michigan than in his state, the Michigan man replies, "On account of the greater sanitary knowledge and intelligence of the people of the state of Michigan."

Some of the wise recommendations of the board have not yet been adopted. Among these we may mention the recommendation made in 1877 that the office of coroner be abolished and that experts be selected to make the physical examinations in cases of persons found dead or suddenly dying.

The board has constantly given intelligent attention to the question of water supply and systems of sewerage. It long recognized the fact that much money is foolishly spent, especially by small cities and villages, in providing these utili-

ties. Recently the board has been given legislative authority to pass upon the water supplies and sewage disposal of various municipalities in the state.

In the eighties, the cheese industry and other milk industries in the state were threatened with serious loss on account of the numerous cases of poisoning with cheese, ice cream, and other milk products. All kinds of theories were offered to explain these accidents. In 1884 the board took up this matter and showed that the poisons formed in milk products were due to bacterial contamination. Now cases of poisoning of this kind are so rare that some people deny that they ever occurred. These researches begun by the board in 1884, led to the suspicion that milk and milk products were accountable for the high infantile mortality. At that time, about 26 per cent of the children born in the state died before they reached one year of age. This was true not only in Michigan but all over the civilized world. The cause for this high infantile mortality was attributed by some to the nature of the soil on which the house was built, by some to the prevailing wind, while others attributed the high death rate to spots on the sun. It was finally shown that the high infantile mortality was due to poisonous milk, and the death rate has been reduced more than half.

In 1884, the board of health with the backing of the Michigan Business Men's Association asked the University of Michigan to build, equip, and man a state laboratory of hygiene. This was not accomplished or at least the building was not in readiness and in operation until 1888. Even with this delay, this was the second laboratory devoted to hygiene and sanitation established in the world, the first being that of the University of Munich which began operation in 1884. In this laboratory suspected food and drink were examined for health officers and for private citizens. Some things happened about that time which doubtless have been forgotten or were never known to the majority now living. The superintendent of a water company in a city in the northern peninsula sent a sample of water to the laboratory for examination. It was reported as unsafe, and the superintendent being financially interested, made no report to the people of this condition. They continued to use the water for about three weeks, during which time many hundred cases of typhoid fever developed in the place. Then the health officer sent a sample of water to the laboratory. He was surprised to receive a telegram that the water had been condemned three weeks previously. The people of the village went after the superintendent of the water works with a rope. Just what happened no one ever knew, but the superintendent has never been seen in that village since.

It is impossible to give any figures showing the number of lives that have been saved, or the financial saving that has resulted to the state from the labors of the Michigan State Board of Health. Whatever credit is due this board during the first thirty or more years of its existence is largely due to a man now living in comparative obscurity, Dr. Henry B. Baker, its efficient secretary during those years. So long as the board had the appointment of its own secretary, the only salaried officer on the board, politics did not touch it. But the time came when politicians became hungry for this salaried position. The legislature was induced to take the appointment of the secretary away from the board and place it in the hands of the governor. From that time on, and so long as it continues, politics has and will continue to seriously interfere with the work of the

board. And now there is a bill before the legislature abolishing the Michigan State Board of Health, making the secretary the sole executive officer, and putting everything in his hands. It should not be understood that there has been no efficient secretary since this change was made, but with every incoming governor the secretary must be changed and scientific carefully planned work can not be done. The bill now before the legislature provides that in place of the State Board of Health there shall be an Advisory Council of Health, but this council has no control over the secretary. If we are going to make the Michigan State Board of Health a political football, let us so declare publicly and have a health commissioner appointed by the governor, responsible only to the governor, and liable to replacement with every change in the gubernatorial office. There is no need of camouflage. Either the secretary should be the whole thing, or he should act under the direction of the board. An advisory council is camouflage; nothing more, nothing less. Crippled as it has been by having no control over its executive officer, the board has done, and is still doing, some most valuable work. The tuberculosis survey of the state, carried out in the years 1915 and 1916, was without doubt the best piece of work ever done in any state in this country or in any country in our fight against tuberculosis. The work which is now being done in combating the venereal diseases is important, and should be continued. A bill has been written, permitting the commissioner of health not only to be the sole administrator of health matters, but to appoint a health officer in every county in the state. This is so plainly political that it has probably died a natural death.

There is complaint made that so few young men are now willing to undertake public health work. The history of the Michigan State Board of Health, and especially that of its long-time and most efficient secretary, is not likely to induce bright and competent young men to undertake such work. As has been stated, the man who did so much for the public health of Michigan, who had labored so long in this field that he was quite unprepared to do anything else, like the faithful old horse, is turned out to live as best he may, and to die uncared for.

—*V. C. V.*

The Catalytic Power of Blood and Solid Tissues

THE remarkable series of papers by Burge* and his associates which have appeared during the past two years on the relation of enzymes, which have the power of releasing oxygen from hydrogen peroxide, to many of the physiologic functions of the body, have awakened considerable interest. These enzymes, which Kastle named "Catalases," have been found by Burge to be intimately associated with the oxidative activity of the body. In general he has found an increase in the catalase content of the blood and tissues of animals in which oxidation is large or has been increased, and a decrease in the normal amount in conditions where oxidation is decreased. He believes that variations in the activity of these enzymes explain one of the physiologic differences in used and

*Burge: Am. Jour. Physiol., see volumes xli to xlviii inclusive.

unused muscle; the difference in the ratio of heat production in large and small animals; loss of weight during starvation and during thyroid feeding; body changes during emotions and during anesthesia; shock; and the cause of the specific dynamic action of foods.

The function of catalase is not known. A number of theories have been advanced; one holds that it destroys peroxides which are formed during the life of the cell and which are harmful to the organism; another that it prevents excessive oxidation within the cell, and still another that it is the substance which releases oxygen from hemoglobin for use by the cell. The work of Burge appeared to indicate that catalase has an important role in oxidation.

Recently Becht† has published a convincing report of work in which he has been unable to reproduce Burge's results. Using what he believes to be accurate and superior methods and making a large number of duplicate analyses he has found a thousand per cent variation in the catalase content of blood of dogs kept under identical conditions, and wide variations in the blood of different species. He noted a decrease in the catalase content of the blood following thyroid feeding, which is exactly the opposite found by Burge; likewise an increase in place of Burge's decrease in the blood during anesthesia. He believes that it is impossible to accurately determine the catalase content of solid tissues by present methods. If Becht's criticism of Burge's work is correct, what appeared for a time to be a master key to a portion of physiology has failed to open the lock.

—*R. G. P.*

The Selective Service Act and Its Lessons

WHATEVER may be said about the functioning of other branches of the War Department, it must be admitted by all that the Provost Marshall General was fully equal to the heavy task assigned to him. He and his assistants deserve every honor that the government can bestow upon them. In April, 1917, when a state of war against Germany was proclaimed, we had a small regular army and the national guards of the different states which had recently been federalized. By June, 1917, these organizations had been augmented by volunteer enlistment to a combined strength of 465,985—altogether too small an army to put into this great war. Indeed it was not deemed wise to provide for an initial army, under training at least, of less than one million. How was such an army to be raised, quickly and with the least disturbance of agricultural and industrial affairs? During two years of the Civil War a half-way conscription was in effect, but it authorized the paying of bounties and the hiring of substitutes. It was resented quite generally throughout the northern states, and in New York it led to a temporary condition of anarchy. The practical result was that it contributed a forced service from only 46,347, out of a total draft of 776,829.

The Selective Service Act of 1917 was wisely enacted, promptly and justly executed, and it gave in the short space of little more than one year an army of more than three million, and had the war continued, this number might have been doubled in another year. The registration, selection, and mobilization

†Becht: Ibid., 1919, xlviii, 171.

moved through all phases with as little friction as could be expected of a newly invented, but scientifically devised machine. The behavior of the National Guard and the National Army on the battle fields of France has demonstrated not only the patriotism, but the fighting efficiency of our newly made and hastily trained soldiers. It is not too much to state that the war was fought and the necessary aid rendered our allies by civilian soldiers, for although seven divisions of so-called regulars participated in the fighting, more than two-thirds of these were recent recruits. These facts should justify inquiry as to whether or not we should choose between a large regular army in which being a soldier is a life work, and universal military training, which would do away with the profession of arms and make us ready at all times and on short notice to raise an efficient army of sufficient size to cope with any emergency that may arise in the future. The advice to disband the regular army and burn West Point, said to have been given by an officer returning from France, is worthy of consideration.

There were 4,557 local boards, an important member of each of which was a physician. For the most part, the doctors on these boards, as well as those on the district boards, did their duty in a commendable manner. It is true that there are stories told of men with glass eyes and cork legs being passed, but the Provost Marshal General makes the following statement in regard to these reports:

"Rumors here and there in the public press stated that the camp surgeons had discovered among the men accepted by the local boards some with glass eyes, some with cork legs, and some with other obvious disqualifications. If such men were found, it is no disparagement for the local board surgeons: for it is safe to assert that such grossly defective persons came from the contingent of about 20,000 men who had never appeared before the local boards, but had been gathered up by the adjutants-general and sent direct to the camps. There is no ground for supposing that the local board surgeons were either incompetent or careless to that extent. The spirit of their practice was to make all intendments in favor of the government; but nothing permits us to suppose that they held or did send to camp any men with cork legs or glass eyes."

It is not denied that the doctors on both the local and district boards made mistakes. They made some, and in the aggregate these grew into many. Nowhere else did the examining physicians fall down in practice more frequently or more sadly than in their failure to recognize tuberculosis. The high death rate in some of the camps from this disease during the first few months of service makes this point incontrovertible. Not only did the doctors on the local boards fail lamentably in this matter, but the experts on the special boards in the camps stumbled frequently and badly, and their mistakes were the more unexpected and the less excusable. It has long been a matter of common knowledge that the ordinary practitioner of medicine is grossly lacking in the skill necessary to detect incipient tuberculosis, but when the man posing as an expert in this disease accepts as soldiers men with the disease so far advanced that death results in less than six months, there is something wrong. Physicians as a rule when they become officers object to being assigned to the examination of

recruits, and doubtlessly many of them perform this function when assigned to them in a perfunctory way, but this is a serious mistake. There is no better opportunity for training in physical diagnosis. When a patient comes to a doctor in civil life, the patient usually partially at least, diagnoses his own case by calling attention to some organ where, in his opinion, his trouble resides. Too often the doctor follows this lead, and gives his undivided attention to the part in question, while the grossest lesions in other parts of the body may pass undetected. This is a fault which the wise physician will soon remedy; even now the more intelligent patients recognize it.

In the first draft, the number of registrants enrolled June 5, 1917, was 9,586,508. This means that, with the exception of the relatively few who were physically unable to report or who tried to evade the draft, there were that many men of draft age in the country.

The number of men actually physically examined in the draft by the boards was 2,510,706, of which 730,756 (29.11 per cent) were rejected. Of those accepted by the local boards and sent to the camps, 5.8 per cent, taking all the camps together, were rejected by the expert boards. During the Civil War, the percentage of rejections averaged about 26 per cent. The Provost Marshal makes the following statement on this point:

"In view of the great advance since that date in standards of medical diagnosis and physical perfection, the foregoing figures indicate a decided improvement in national physical condition during the past two generations."

So far as the study has been made, there is practically a tie in the percentage of rejections as between urbans and rurals. Attempts to deceive the medical examiners were made only to a slight and negligible extent. The report states:

"Here and there a local board reports a locality as showing 50 per cent of attempted falsifications, but these instances were sporadic and represent some local obliquity of morals."

In the report it appears that venereal diseases were accountable for only 4.27 per cent of the rejections, but this does not correctly indicate the prevalence of these diseases among the men because unless the man was rendered quite unfit or was a positive danger to others, these diseases fortunately did not warrant rejection. Had this been the case, the percentage of rejections from this cause would have been much higher. Statistics show that venereal disease is much more prevalent among civilians than among soldiers. It has been positively demonstrated that instead of civilian communities needing protection against soldiers so far as venereal diseases are concerned, the soldier needs protection from civilian communities. In the record as it stands, it appears that defects of the eye and of the teeth were most numerous. It is gratifying to note that alcoholism and the drug habit were infrequent. Mental deficiency and nervous disorders show up rather alarmingly.

The ratio of physically qualified to physically examined was less than 60 per cent in Maine, Rhode Island, Vermont and Pennsylvania; from 60 to 65

per cent in New Hampshire, West Virginia, and Massachusetts; from 65 to 70 per cent in New York, Kentucky, New Jersey, Louisiana, and Nevada; from 70 to 75 per cent in Maryland, Virginia, North Carolina, South Carolina, Georgia, Florida, Mississippi, Arkansas, Tennessee, Missouri, Illinois, Indiana, Ohio, Michigan, Wisconsin, Colorado, New Mexico, California, Oregon, Washington; from 75 to 80 per cent in Alabama, North Dakota, Nebraska, Kansas, Oklahoma, Texas, Arizona, Utah, Wyoming, Idaho and Montana; 80 per cent and over, in South Dakota. It is doubtful how much stress can be placed on these figures. As they stand, they indicate a physical inferiority in New England and Pennsylvania, even when compared with the Black Belt of the South, and this is more striking when the comparison is made with the plain and mountain states of the West. The Provost Marshal General says:

"The causes for rejection when ascertained will be of great sociological and medical value, but in the present emergency the time and labor to examine in detail two and one-half million records can not be spared."

Of the 3,082,949 called by the local boards, 252,294 (8.18 per cent) failed to appear for examination. Of these at least three classes were not "slackers": (1) Many enlisted after registration but failed to notify their local boards of their enlistment; (2) some died; (3) many were transferred to other boards but were not so reported. The numbers estimated as belonging to these classes are (1) 85,000; (2) 750; (3) 1500. This leaves about 150,000 to be accounted for. It is believed that 100,000 of these were aliens. Many, especially those living along the Canadian border, passed over the line, preferring to serve with their native armies. Other aliens were so ignorant that they did not understand. The real "slackers" are estimated at about 50,000, an average of about 10 for each local board.

The question is asked whether the physical requirements as set forth by the Surgeon General were too strict or not. The Provost Marshal General remarks:

"On this point the civilian surgeons have expressed varied opinions. A large majority say that the physical requirements are not too exacting, but a considerable number deem the physical requirements too strict in many respects, notably as to the weight and height relation, teeth, eyes and feet, and contend that the regulations as strictly applied tend to exclude many capable and efficient men.

"For example, one board cited a case of exclusion for flat-foot of a man who had for many consecutive seasons endured the hardships of a guide vocation in the Canadian forests, and the prevalence of flat-foot among the sturdy negroes in the South was frequently commented upon."

As to flat-foot as a disqualifying condition, even orthopedists are divided. But that, on the whole, the requirements were not too strict—indeed were not strict enough—is shown by the large numbers that subsequently had to be transferred to development battalions. Defects in teeth, eyes, and in many other particulars should have been remedied in civil life when these boys were in school. The nation that is not interested in the physical education of its children is not prepared for full and satisfactory achievement in either peace or war.

It will be of interest to inquire briefly into the claims for exemption. On this point the Provost Marshal General states:

"Of the total number called (3,082,949) 1,560,570 (50.62 per cent) made claims for exemption. Of the claims made 1,215,049, or 39 per cent of the persons called, or 77.86 per cent of the claims made, were granted. Of 1,419,678 claims made to local boards, 1,161,206 were granted; that is 81.79 per cent of claims made before local boards were granted; 140,892 claims were made to district boards and 53,843, or 38.21 per cent of claims made were granted. * * * Of the total claims granted (1,161,206) 859,150 or 73.99 per cent of all claims granted were on the ground of dependency, 228,452 or 19.67 per cent were on the ground of alienage, 67,716 or 5.83 per cent were on the ground of vocation, 3,887 or .34 per cent were on the ground of religious belief, and 2,001 or .17 per cent were on the ground of moral unfitness."

In considering these figures, it must be borne in mind that the national purpose was to assist our allies, not only with armed forces but industrially in the manufacture of munitions, guns, airplanes, ships, automobiles, etc., and with food. Therefore it was not only necessary to make soldiers, but to keep the wheels of industry going and at the same time to produce enough food to supply ourselves and our allies. We were compelled to provide for military, agricultural and industrial needs. Since the world began no nation has been wise enough to make an equal distribution of the burdens of war among these classes. War has always given opportunity for heroic sacrifice on the part of some, and selfish gain on the part of others. In the first flush of patriotism the doctor who for any reason was compelled to stay at home promised to divide his fees with the families of brother practitioners privileged to go. We may now ask ourselves to what extent this good intention has been realized. At first, the manufacturer of munitions stated that he would seek no large gains,— and so it ran through all occupations and callings. We may never know to what extent this altruistic spirit has dominated in actuality. However, man has not yet acquired the wisdom necessary to run the governmental machinery with equal justice to all, and with our many shortcomings the first real conscription attempted by this country has been fair in its application, prompt in its execution, and efficient in its results.

The Provost Marshal General's optimism concerning the physical improvement of the nation since the Civil War has questionable support in facts. Be this as it may, the following are some of the lessons which seem to be indicated by our experience with the draft:

(1) At least one-third of our young men are unfit physically for military service. If those who proved unfit after trial were added, this fraction would be much larger. This is the real test of any man's fitness for military service. The number of unfit, under any estimate, is too large and indicates lack of proper physical training, or the presence of unsanitary environment, or the inheritance of marked physical defects. Doubtless all of these are factors contributing to this delinquency. The causes should be ascertained and steps taken for their removal.

(2) We have among us too many low-grade aliens. So far, the records fail to show to what extent the alien stock among us has contributed to our physical

defects, but the facts given concerning the relative ratio of physically qualified to physically examined are suggestive at the least. If the average physical condition of the young men of Alabama with its large negro population is better than that of Pennsylvania with its large foreign white population, it is time that greater restrictions should be placed on immigration. The report does not give sufficient data on this point, and we await details concerning rejections for physical disqualifications.

(3) We certainly should take it to heart and recognize that, so far as the physical training of our youth is concerned, we are sadly at fault.

—*V. C. V.*

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ORIGINAL ARTICLES

ORGAN EXTRACTS*

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HISTORICAL REVIEW

In 1888 Brieger isolated a specific, active, toxic substance from the amputated arm of a victim of tetanus. In the year following Brieger and Frankel noted the toxalbumin in broth cultures of B. Tetani. Kitasato in 1891 injected the blood of tetanus infected laboratory animals into other animals, and Nissen did the same with blood from patients dying from a tetanus infection, whereby both were able to observe its toxic action. Brieger's pupil, Immerwahr, went a step farther than his teacher and isolated a toxalbumin from the organs of infected laboratory animals which he assumed to be identical with the product from the bouillon cultures. He likewise isolated the same substance from an amputated human leg. Stern in 1892 demonstrated the toxic activity of the blood of tetanus patients fifty-four hours before their death. Then a large number of workers began to investigate the blood stream of human beings under all sorts of pathologic conditions as well as in health. Rabbits were used as recipients and the M.L.D. of normal human blood varied among some fifteen workers between 8 and 27 c.c. per kilogram of rabbit. The blood of sheep, swine, the ox and horse were likewise injected and their toxicities determined.†

Uhlenuth[1] in 1897 reviewed these divergent observations, and after amplifying laboratory trials to include a number of new diseases and pathologic conditions, concluded that positive animal reactions to the injection of blood could not be relied upon as differentiating between a normal and a pathologic con-

*From the Hygienic Laboratory, University of Michigan.

†Quoted from Uhlenuth: Ztschr. f. Hyg., 1897, xxvi, 384-397.

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dition of the donor's blood. He made his injections subcutaneously on guinea pigs and found that all blood, in greater or less quantity, caused infiltrations at the site of the injection when in small doses, with necroses followed by death when the doses were relatively large. Normal horse serum was the least toxic and almost without effect up to a dose of 20 c.c. when an easily resorbed infiltration was evident. Obduction of dead animals disclosed nothing of any importance except in the animals dying from an injection from a scarlet fever patient, when a cloudy swelling of the kidneys was noted, accompanied by incipient fatty changes.

In 1898 Brieger and Uhlenuth made inquiry into the nature of the toxic agent that seemed to be present in all bloods, and decided that it had nothing to do with the fibrin ferment of Schmidt and Pekelharing, or with any other ferment that they knew anything about, and that it did belong to the toxalbumins, since it was readily destroyed by alcohol, and was refractory to dialysis and filtration through porcelain. They next tried the effect of placing a bit of homologous tissue under the skin, and found that similar necroses developed, usually ending in the death of the animal. A physiologic salt suspension of the tissue was found to be equally effective. Greatly to their surprise, when they extended their work to the heterologous tissues, they found that the tissues of the horse, to whose serum the animals failed to react, were very powerful in their necrotic effects. On the other hand no differences could be detected in the effects of normal human or pathologic tissues of any sort. Plunging into this work with considerable energy they soon found that a more thorough preparation of the tissues before placing them under the skin permitted them to be absorbed without appreciable effects, so they dropped the work at that point.[2]

In 1909 Schenk[3] expressed a liquid from placental tissue which had a toxic action upon intravenous injection into rabbits. He was seeking some light on eclampsia. He found that a short incubation with a small quantity of serum from varying sources sufficed to completely detoxify the expressed liquid. Inactivation of the sera did not affect their ability to render harmless the extracts. He was able to secure a short immunity to as high as three lethal doses by the usual process of repeated sublethal injections.

Kraus, Volk, and Lowenstein[4] in 1911, working in the field of tuberculins thought that animals infected with tuberculosis showed a marked susceptibility to a liquid which they had expressed from the organs of tuberculous laboratory animals. However, further researches showed that there was no specific susceptibility on the part of the infected animals, and also that liquids expressed from the organs of healthy animals served to produce the same necroses and deaths.

In Dold's[5] initial paper he reviewed much of the work that has been mentioned and confirmed that of Volk and Lowenstein in particular. He worked with physiologic salt extracts and pointed out that the toxicity of the extracts varied directly with the quantity of tissue employed or inversely to the amount of salt solution used. He found that the intraperitoneal or subcutaneous dose

was from three to four times that required by intravenous injection for the same result, and that the homologous species was relatively more susceptible to the different tissue extracts than heterologous species. He further noted that extracts lost their toxicity not only by standing at room temperature for a few days, again confirming Volk and Lowenstein, but also by heating to 60° C. for not less than thirty minutes. Such heating caused the formation of a precipitate, the decrease in toxicity being parallel with the mass of the precipitate that was thrown down. Filtration through a Berkefeld also rendered Dold's extracts nontoxic; but Aronson[6] had already noted this point in 1909 in connection with an extract of beef kidneys that he had prepared for the treatment of kidney disorders. Dold also used serum for the detoxification of extracts without acknowledgment of Schenk's earlier work which provoked a polemic concerning the priority of the work on organ extracts. Schenk[7] claimed that his "Pressäfte" was a general principle and that Dold had done nothing new when he substituted extraction for pressure or extended the work to other tissues. However, Dold did determine more closely the quantity of serum that would detoxify an extract and found [31] that so small a quantity as .5 c.c. in contact with a lethal dose of the extract for fifteen minutes completely neutralized its effects. In continuing his work Dold[8] noted that all sera were not equal in their power for detoxification, but speaking broadly, the homologous serum with the tissue was most effective. No definite law could be formulated because all sera in some proportion would minimize the toxic effect of all extracts. Filtering the sera through porcelain completely eliminated their power to remove the active agent from the extracts. Dold believed the process of detoxification to partake of the nature of a ferment inhibition, pointing in support of this view to the work of Hedin[9] who had observed that the addition of egg or seralbumin to a casein-trypsin mixture hampered digestion, and that the inhibition was more complete when the order of combination was trypsin-albumin-casein. Dold further showed that complement did not enter into the neutralization process, for by appropriate titration, complement was shown to be undiminished in a serum that had been used for detoxification as compared to an unused portion of the same serum.

Incubation with kaolin removed the toxicity of the extracts, and Izar[14] later showed that brain emulsion, talcum, animal charcoal, and rice starch would in particular amounts for each substance render the extracts harmless. When Dold attempted to immunize rabbits by successive sublethal doses the animals rapidly became cachectic and died at varying intervals. The best he could do was to obtain a very feeble resistance to one lethal dose in some animals. This is in marked contrast to Schenk's earlier claim of immunity to three lethal doses of his expressed liquid.

Inquiring into the source of the toxic substance that seemed to be ubiquitous for animal tissues, Dold[10] assumed that it had its origin in either the body cells or in the lymph. He could obtain but weakly toxic extracts from washed leucocytes or erythrocytes, and injections of relatively large quantities of either the fresh cells or the cell residues after extraction, failed to produce

an effect that was at all comparable to that of the tissue extracts. The animals died, but the preliminary symptoms were not the same and the deaths were delayed a considerable time as compared to the three to eight minute deaths of the animals receiving the tissue extracts. Dold dissected ox and rabbit eyes into their components and made extracts of the separate parts. He found the toxicity of these extracts to be parallel with their cell content. The order of toxicity in a descending scale being, uvea and retina, sclera, cornea, lens, and vitreous humor, the latter two being entirely without effect. He explains the apparent discrepancy between these findings and his assertions concerning the red and white cells by calling attention to the more strict metabolic activities of the tissue cells as compared to the functions of the blood cellular elements. Cutting a rabbit's lung into three pieces, he allowed it to remain in physiologic salt solution for two hours. After removal of the lung the solution was centrifuged, and upon injection proved to be as toxic as if the tissue had been rubbed up as was his usual custom. His conclusion as to the source of the poison is best expressed by his statement: "An extractable poison is in animal tissue in a quantity proportional to their metabolic activities and lymph content."

Animals receiving a lethal dose of organ extracts present the characteristic features of the anaphylactic syndrome. However, obduction shows clots in the heart, accompanied by abdominal hyperemia and thrombi in the lungs. Dold believed the thrombi to be the cause of death. In order to test the point he added Jacoby's hirudin to a lethal dose of the extract or else gave the animal an injection of hirudin just preceding the injection of the extract. The clots were not found in the lungs in spite of the fact that the animals died. This indicated that the supposed thrombic enzyme did not play the part assumed by Dold. A further use of a more freshly prepared extract of leeches not only saved the animals, but presumably prevented the formation of the thrombi. One can therefore form his own conclusions as to the formation and influence of the thrombi, since Dold did not attempt to further clear up the point. He found that ten per cent peptone administered in varying quantities just before the injection of the extracts saved, from a considerable series of experimental animals, an average of 75 per cent.

Bauer and Wüstoff[11] considered organ extracts to be equivalent to anaphylatoxin as prepared *in vitro*. Dold proposed the same notion and even thought that tissue from anaphylactic animals yielded a more typical anaphylatoxin.[32]

Gräfenberg and Thies[12] made a physiologic salt extract of testicles and found it to be quite toxic. They were interested in the specificity of tissue reactions as compared to species reactions to such extracts. They found that males of the same species were slightly more susceptible than any normal animals; females of the same species were highly resistant. Young animals of the same species showed no sexual differences in their reactions to the extracts. The most susceptible animals to the homologous testicular extracts were castrated males and pregnant females. Sensitized animals, which they were able to secure by careful manipulation, reacted promptly to an injection of any

extract. They could find no grounds for a species specificity, but believed their work to point to a possibility of tissue specificity to testicular extracts. Izar and Faguioli[13] made a methyl alcohol extract of bovine and dog testicles and injected into rabbits and pigs a watery emulsion of the extracted lipoids. They used a long series of dilutions and observed but slight evidences of toxicity. Heating such emulsions for one-half to one hour at a temperature of 50° C. raised their toxicity very markedly. Carrying the heating on up to a temperature of 100° C. for ten minutes still caused an increase in toxicity, but if heated longer at this higher temperature, the toxicity fell below that for the unheated extracts. A previous injection of .8 to 2.5 c.c. saturated sodium chloride containing one per cent of calcium chloride protected rabbits from death in most cases and always prolonged it. Titration of complement before and after injection of their watery emulsions showed a marked decrease following the injections, and the decrease was in general parallel to the severity of the reaction to the emulsion. They confirmed Dold's failure to secure immunity.

Izar and Ascoli[30] and later Izar[14] alone, worked with lung extracts of pigeons, sparrows, and rabbits. They noted the temperature reactions and found them to be typical for the parenteral injection of proteins. They extended the attempt to protect the recipient animals by a previous or simultaneous injection of inorganic salts, using salts of barium, strontium, magnesium, potassium, ammonium, and cadmium. Such protection as they were able to observe they ascribed to the cations involved. The various salts were not uniform in their effects and they found calcium chloride the most effective, because it lowered the toxicity more and therefore kept the temperature curve more nearly normal. They found serum from well fed animals to be most potent in detoxification; although serum from starved animals was not without considerable effect in lowering toxicities and therefore assisting in the maintenance of a more nearly normal temperature curve. Later work by Izar and Patane[15] throws interesting light on Dold's conclusions concerning the source of the poison. They made the usual extract of rabbit's lung and proved its toxicity. The tissue residue from the original extraction was then washed in several liters of physiologic salt solution in successive portions, all the washings being discarded. Then the original technic was repeated on the tissue and the extract thus made proved to be nearly as toxic as the original. Again, the lungs of a freshly bled rabbit were removed and an extract made from one immediately. The other was perfused with salt solution until it was white and bloodless, and then extracted. When both extracts were tested for their toxicity, that from the perfused lung proved to be the more toxic. They found it impossible to secure a toxic extract from the dried and powdered lung with methyl alcohol, although Fischer[16] could detect no differences in the properties of a physiologic salt extract of fresh and dried tissue. Izar and Patane incubated the physiologic salt extract of lungs at 37° C. and found that the toxic principle was quantitatively bound to the precipitate that was thrown down. Continuing Izar's previous work on the protection afforded by the inorganic salts, they were able to neutralize *in vitro* by the addition of tenth normal cal-

cium chloride. However, if to such a neutralized extract they added an exact chemical equivalent of potassium oxalate the toxicity was restored. Their earlier work had shown that potassium ions were low in protection as compared to the ions of calcium.

Fischer could not confirm Dold's observation that standing a few days at room temperature sufficed for the extracts to lose their potency, as his were effective after standing for eight weeks. He asserted that there were two substances that influenced the clotting of blood; one that hastened, and another that delayed the formation of a clot. Therefore, the obduction findings will depend on which phase of these influences was predominant when the animal died. The quantity of extract was but a minor part in the actual working out of its effects, and we are told that the exact nature of the substances that control the blood clotting is as yet unknown.

Distaso[17] worked with material secured from cadavers, also with fresh tissues of laboratory animals. He shortly abandoned the cadaverous material as he satisfied himself that their toxicity was a result of a bacterial activity after death. He found tissue extracts to be heat labile, inactivated by serum, and rendered harmless by filtering through porcelain, thereby confirming Dold's work on these points. He also reported that precipitation with alcohol destroyed the toxic agent; that treatment with fibrin or gelatine markedly lowered their effects, and that dialysis completely inactivated his extracts through the loss of salts. Before abandoning the cadaverous material as a source of tissue extracts, he worked out some of their properties, and since they were almost parallel for those of a ferment such as diastase, he concluded that the active principle of extracts was a colloidal ferment. Later he made a comparative study of extracts made from the lungs and intestines of a female rabbit and her fetal young. He found that the lungs of both yielded a toxic extract, but the intestines of the mother only did so. He argued that this showed the active principles of lung and intestinal extracts to be dissimilar, and that intestines gave a toxic extract by reason of the processes of extra-uterine life. Dale and Laidlaw[19] isolated B-iminazolylethylamine from colon tissue. Its action is very similar to Distaso's intestinal extracts, but it is heat stable, so can not be the same product. Roger[18] found that bile and pancreatic fluids, injected separately or together were highly toxic for the homologous animal. Further, Roger[20] and Falloise[21] have shown that the poisonous material contained in feces is more marked in the excreta of a breast fed infant than from an adult, and that feces of a normal adult are more powerfully toxic than from a typhoid fever patient. In all cases extracts of fecal material were heat stable.

Ichikawa[22] in 1913 studied the blood clot accelerating effects of various extracts *in vitro* and found this property to run parallel with their toxicity. He was unable to confirm Dold's assertions that the extracts were most toxic for the homologous animal and that homologous serum was most effective for detoxification. He found that sodium citrate had an effect analogous to hirudin either by previous or simultaneous injection with the extracts. He evidently considered organ extracts to be equivalent, in their effects at least, to anaphy-

latoxin, for he remarks that the temperature changes produced by injection of Friedberger's anaphylatoxin and of appropriate amounts of organ extracts are identical. Injection of large, but sublethal doses of lung extract, caused marked leucopenia; smaller doses caused an incipient leucopenia which soon reversed itself and ended in leucocytosis. Blood pressure remained unaltered by the injection of sublethal doses. No agglutination or precipitation of homologous red cells by lung extracts could be observed by Ichikawa, although Embleton[23] was able to note an appreciable rise in the hemolytic power of serum from rabbits that had received a sublethal dose of some organ extract. It will be recalled that Dold was able to detoxify his extracts by heating to 60 C. for not less than one-half hour; Ichikawa confirmed this point for rabbit lung extract, but that from the lungs of the guinea pig withstood this temperature without any diminution of toxicity. Aronson,[24] in attempting to prepare anaphylatoxin without the use of serum, heated bacterial cells in physiologic salt suspension to a temperature of 65° C. and secured a toxic filtrate by centrifuging out the germ substance. If bacteria are chemically equivalent to the extracts of tissue and one can rule out the possibility of the extraction of an endotoxin, that would be heat stable to the temperature employed, it would then be in order to use Aronson's work in checking up other results with organ extracts. Ichikawa gave support to the dual nature of the extracts as suggested by Fischer, by attempting to immunize rabbits with a heat neutralized extract. The heating eliminated the toxicity, with its accompanying blood clotting changes, but the animals all developed cachexia and died just as if they had been given sublethal doses of the unheated extract.

Dold and Kodama[25] in a later work indicate that all their extracts were acid in reaction, and that they were not able to modify their toxicity by either making alkaline or slightly more acid. A precipitate settled out upon stronger acidification which was found to carry the toxic agent with it, thereby confirming Izar and Patane in a similar observation. This precipitate could be kept dry for one month and the toxin recovered by water, ether or acetone. Addition of fresh sera to the dried precipitate, followed by removal and an immediate extraction of the substance by water showed that the sera had destroyed the toxic principle. They also added their confirmation as to the effect of alcohol on organ extracts as announced earlier by Distaso. Treatment of an aqueous extract with magnesium sulphate partially salts out the toxic substance, which could be recovered salt free by dialysis. Seeking more knowledge concerning the chemical identity and nature of organ extracts, Dold found that treatment with ether caused a separation into a watery layer on the bottom, with a precipitate above, and the ether on top of all. When very strong extracts were so treated a part of the poison was found in the precipitate, but if an extract of only moderate toxicity was handled with ether the poison was found to have been destroyed. Similar treatment with acetone always destroyed the poison, regardless of what strength of extract was used. Since these same characteristics are also common to ferments, they were held to be additional proof of the probable ferment nature of the extracts.

Catapano[26] and Bittorf[27] examined a large number of extracts of animal and human tissue for their mydriatic properties. The adrenals were the most active but all tissues with exception of thyroid, spleen, and nerve yielded an extract of greater or less activity. Bingel and Strauss[28] confirmed these workers in all their findings except for the kidney and liver. All were agreed that the extracts, as far as their mydriatic properties were concerned, were stable to heating, and the last mentioned workers claimed serum to be without effect on this characteristic. Dold[29] probably had occasion to note the same effects on the eye as these workers, because he does mention a marked inflammatory process that he had observed to come on very rapidly, which slowly subsided.

EXPERIMENTAL

First, a brief resumé of the circumstances that provoked this study will be of some interest. In the course of a series of experiments we had occasion to attempt to determine the fate of Vaughan's poisonous protein cleavage product when administered enterally to cats. The presence of the poison in the blood stream was definitely established by heart punctures following its introduction into the stomach by a tube. By withdrawals of heart blood from a dosed cat at intervals of ten to twelve minutes, followed by immediate transfer of such blood to guinea pigs intravenously, a wave of toxicity could be noted that rose to a peak in about one hour and then gradually faded away. This observation was carefully checked by the injection of normal cat's blood. Following the matter one step farther, it seemed in order to see if any of the poison could be recovered from the tissues of such an experimental animal after it had been repeatedly dosed with the poison. For reasons which need not be given here alcoholic extraction of the tissues, followed by appropriate after-treatment of the extract was the method of procedure. Obtaining an extract that was highly toxic to guinea pigs upon intravenous injection it was interpreted as evidence of poison recovery. However, upon applying the identical technic to the organs and tissues of a normal cat an extract was secured that was equally toxic to the recipient guinea pigs, as the extract from the tissues of a dosed cat. Blocked, for the time at least, by this unexpected result, a study of the toxic properties of organs and tissues was undertaken.

Methods Employed.—It will save repetition if the details of the method of extracting the tissues are given at this time. What we have already referred to as the "extract," and will have frequent occasion to refer to again, was prepared by the following procedure:

Animals were killed by thorough exsanguination. Such tissues as were desired were immediately removed and placed in separate receptacles. They were washed, under the tap, free of all blood, and all fat and extraneous tissues were removed from each organ. The stomach and intestines were opened up and well cleaned. By the use of an ordinary household food chopper the tissues were ground to the consistency of a fine sausage. In this condition the tissues were placed, always in separate vessels, under absolute alcohol. The quantity of alcohol was 2 c.c. for each gram of the moist ground tissue. For this purpose Erlenmeyer flasks were used, stoppered with a plug of cotton.

They stood at room temperature with their contents for periods varying from two days to five weeks, occasionally being shaken. At the conclusion of this extraction period with the alcohol it was recovered. This was accomplished by pouring out the flasks upon a clean unstarched gauze supported in a funnel. This funnel was so arranged that the fluid passed onto a qualitative filter paper supported in another funnel below the one containing the cloth. The tissue was well squeezed out by hand compression in the gauze. The alcoholic filtrate was received in a large evaporating dish. The alcohol was driven off on a steam bath, the evaporation being carried nearly to the point of dryness. The residue left in the dish was then taken up either with physiologic salt solution or with distilled water, usually the latter. Macroscopically nothing seemed to be dissolved out of the residue by this treatment. However, color was imparted to the liquid, and this varied in intensity with the tissue concerned. This liquid was cleared by filtration through paper, and the amount of water or of salt solution added was so manipulated that the final volume of the filtrate represented two grams of the original moist tissue to each c.c. The secondary or final extraction fluid was refractory to filtration. This was especially marked in the extracts from the abdominal viscera. In order to obviate this difficulty recourse was sometimes taken to passing the liquid through a plug of glass wool in order to eliminate the larger part of the material in suspension. This filtrate was centrifuged at eight thousand R.P.M. for ten to fifteen minutes. This substitution of centrifugation for filtration produced no essential change in the characteristics of the extracts other than an increased clarity. Evidently whirling at the high speed available would throw down some particles that would pass a filter paper. This was shown to be so by centrifuging an extract that had originally been filtered. A very slight deposit was observed in the centrifuge tubes, accompanied by the change in clearness. However, no change whatever was detected in the toxicity of an extract after such treatment. This final watery solution of such materials as may have been dissolved out of the residue left upon evaporation of the alcoholic extraction liquid, is what we have designated as the extract. In all cases, except as shall be hereafter indicated, it was prepared as outlined.

Method of Testing Toxicity.—The guinea pig was used as the animal of choice for testing toxicity. This animal reacts promptly to injections of toxic substances, and generally with consistency. However, in tabulations of experimental data that are to follow, some instances will be noted where guinea pigs of approximate weights reacted differently to equal doses of the same extract or of other toxic substance. One must therefore consider that individual variation is still playing some part even in as highly susceptible an animal as the guinea pig. This accords with the experiences of others on the same point.[33] The place of injection was into one of the external jugulars, usually the left, the Latapie animal board being employed as a holder. The vessel mentioned is reached readily and nearly bloodlessly by a properly placed superficial incision.

Since the guinea pigs used as recipients for the extracts displayed the true anaphylactic syndrome it will be in order to briefly outline the interpretation of the phases used in tabulations to describe their responses.

Nil means a failure to react. Included in this group are all animals that show only an accelerated breathing rate by reason of the excitement of handling. Distinct pumping was lacking.

Light shock indicates some peripheral irritation, accompanied by hyperexcitability, slight dyspnea and jerks.

Moderate shock conveys the picture of a very rapid passage of the preliminary stages immediately followed by spasms and marked air hunger. The animal if thrown did not remain prostrate, but was soon on its feet again.

Violent shock and *near death* are differentiated only by the severity of the prostration. In those cases where the shock is apparently of maximum intensity, but the animal after a short period of prostration recovers promptly and fully, the first term is used; but when the prostration is long drawn out, during which time there may be some question as to whether the animal is dead or alive, the latter expression is employed.

The twitching of the nose that is so characteristic of anaphylactic death was used to mark fatal termination. Figures given under the result heading in the tables always indicate the death of the animal and give the elapsed time from the completion of the injection to the last nasal twitch.

Autopsies were invariably performed and are only commented upon when the obduction shows something at variance with the typically distended lungs, beating heart, fluid blood and hyperemia of the abdominal viscera.

Distribution of Extractable Poison in Tissues.—It was thought desirable in the beginning to subject a wide range of tissues to the extraction process, and note the occurrence of the toxic agent. By adhering to the same technic it would be possible to make observations as to the probable quantity of the poison present in the tissues examined. The results of this phase of the problem are conveniently summarized in Table I.

The tissues represented in Table I are sufficiently heterogenous, in both respect to species and organs, to warrant the belief that the extractable poisonous agent of tissue is present in all animal tissues to a greater or lesser extent.

Quantity of Material Extracted from the Tissues.—When the alcoholic extract was evaporated the mass of the residue left in the dish was slight. It formed but a very thin coating on the bottom and sides of the dish. It has already been remarked that the treatment of this residue with water did not dissolve any appreciable quantity of it. It was decided to get some exact information as to the actual quantities of material being extracted by the alcohol from the tissues. We wished further to know how much of this material was dissolved by the water, and to determine the amount of solids held in solution in the extract as injected into the guinea pigs. Accordingly, measured amounts of the alcoholic extract were evaporated to dryness on the steam bath and the weight of the residues determined. The same process was carried out on the extract as injected. From these figures it was but a simple procedure to calculate the total residue from a given amount of tissue and therefore the percentage of material that was being extracted. It is obvious the same information could be obtained concerning the extract as it was injected. It will be noted that the concentration of the final extract is expressed in terms of milligrams per cubic centimeter. Table II gives the data on the point under consideration.

The data in Table II are from the tissues of the cat. They are identical with the tissues of the cat the toxicity of which is given in Table I. It is possible to make a comparative study between the amounts of solids that are being injected and the toxicity of the extract. This will be taken up later.

TABLE 1

SHOWING THE DISTRIBUTION AND RELATIVE TOXICITY OF A POISONOUS EXTRACTABLE SUBSTANCE IN TISSUE

SOURCE		GUINEA PIG		C.C. INJECTED*	RESULT
ANIMAL	TISSUE	NO.	WT		
Cat	Stomach	1	175	5	3′
		2	175	3	2′
		3	180	1	Light shock
	Intestine	4	150	5	4′
		5	180	1	Light shock
	Liver	6	230	5	Violent shock
		7	190	3	Moderate shock
		8	160	1	Nil
	Kidney	9	235	5	Violent shock
		10	200	3	Violent shock
		11	215	1	Light shock
	Spleen	12	160	5	2′
		13	200	1	Nil
	Lung	14	245	5	Moderate shock
	Heart	15	190	5	Light shock
	Muscle	16	215	4	1′ 30″
		17	205	2	Near death
		18	250	1	Nil
	Brain	19	190	5	2′
		20	200	2	Nil
Rabbit	Muscle	21	155	3	2′
		22	180	1	Nil
		23	240	2	Near death
	Stomach	24	225	3	Moderate shock
		25	210	4	4′
	Heart	26	175	4.5	3′
	Spleen	27	205	4.5	Violent shock
	Brain	28	190	4	2′
	Lung	29	210	4	2′
	Kidney	30	205	4	4′
		31	175	1	Nil
	Intestine	32	180	3	Light shock
		33	220	4.5	Moderate shock
	Liver	34	210	4.5	1′ 30″
		35	190	2	Moderate shock
Dog	Muscle	36	200	2	Violent shock
		37	235	3	Near death
		38	250	4	4′
	Brain	39	205	4	5′
		40	175	3	Near death
Guinea Pig	Stomach	41	160	3	Violent shock
		42	165	4.5	1′ 30″ Clot in heart
	Intestine	43	175	3	Near death
		44	215	4	Near death
		45	185	4.5	2′ Clot in heart
	Liver	46	200	4.5	Near death
	Kidney	47	170	4.5	1′ 30″
		48	185	2	Moderate shock
	Spleen	49	200	4 (5 gm.)	Nil
	Lung	50	205	4.5	30′
	Heart	51	200	4 (7 gm.)	1′ 30″
	Muscle	52	250	4	2′
		53	215	2	Light shock
		54	185	3	Near death
		55	185	4	Violent shock
		56	180	4.5	Near death
	Brain	57	180	4.5	2′
		58	155	2	Moderate shock

TABLE I—CONT'D

SHOWING THE DISTRIBUTION AND RELATIVE TOXICITY OF A POISONOUS EXTRACTABLE SUBSTANCE IN TISSUE

SOURCE		GUINEA PIG		C.C.	RESULT
ANIMAL	TISSUE	NO.	WT.	INJECTED*	
Sheep	Muscle	59	175	2	2′
		60	175	1.5	Moderate shock
Veal	Muscle	61	180	2	Near death
		62	200	2.5	3′ 30″
	Liver	63	210	4	4′
		64	210	3	3′
		65	170	2	Light shock
Ox	Muscle	66	200	2	Violent shock
		67	180	2.5	3′
		68	170	2	4′
	Liver	69	160	2	Violent shock
		70	175	2.5	Near death
		71	250	3	Violent shock
		72	230	4	2′ 30″
Hog	Muscle	73	175	2	Violent shock
		74	165	2.5	3′

*Each c.c. represents 2 gm. of tissue.

TABLE II

SHOWING THE AMOUNT OF MATERIAL EXTRACTED FROM THE TISSUES OF THE CAT AND CONCENTRATION IN FINAL EXTRACT

	ALCOHOLIC EXTRACTION			EXTRACT AS INJECTED		
Tissue	Wt.	Wt. of residue	% of tissue	Wt. of residue	% of tissue	mg. per c.c.
Stomach	69	0.934 gm.	1.55	0.283 gm.	0.47	9.44
Intestine	195	2.621	1.34	1.772	0.91	18.17
Liver	150	4.85	3.23	2.315	1.54	30.80
Kidney	62	0.934	1.51	0.805	1.30	25.90
Spleen	23	0.372	1.61	0.181	0.79	15.75
Lung	52	0.765	1.47	0.300	0.58	11.53
Heart	25	0.381	1.52	0.163	0.65	13.00
Muscle	350	8.275	2.36	6.406	1.83	36.60
Brain	67	1.410	2.10	0.732	1.09	21.85

Reaction of the Extracts.—The reaction of the extracts was usually markedly acid to litmus. Occasionally an extract of stomach or of intestinal tissue would be neutral to litmus. No ready explanation of these exceptions was apparent. The color of the extracts made it necessary to use litmus in titrating their acidity. The method of titration was to add in succession small amounts of standard alkali. Between each addition of alkali pieces of both red and blue litmus paper were applied to the solution. These were arranged on a clean glass plate, each pair being placed opposite each other and in exact order of use. The addition of alkali was continued until the reaction was clearly alkaline by both pieces of litmus. The litmus paper series passed from both red at one end to both blue at the opposite end of the series. When the strips of paper were air dry they were inspected and the neutral point was determined

by selecting from about the middle of the series that pair of papers that had the same tint. The total alkali added up to this point was therefore a measure of their original acidity. In Table III the acidity is expressed in c.c. of normal alkali required to exactly neutralize 100 c.c. of the extract. In the actual titration a more dilute alkali was employed, and the results were then calculated to the basis mentioned.

TABLE III

ACIDITY OF CAT TISSUE EXTRACT

TISSUE	C.C. NORMAL ALKALI REQUIRED TO NEUTRALIZE 100 C.C.
Intestine A	2.88
Intestine B	1.88
Liver A	2.71
Liver B	2.40
Liver C	1.81
Lung A	0.34
Lung B	1.77
Stomach A	0.67
Stomach B	1.60
Brain A	0.40
Brain B	2.43
Kidney A	2.50
Kidney B	2.73
Kidney C	2.00

The letters indicate that an extract from a different animal was being tested, although from the same tissue. Guinea pigs are susceptible to injections of acid solutions. It was thought that the acidity of the extracts might be the ruling factor in their toxicity. But no lack of toxicity was found in those extracts of stomach and intestine that were found to be neutral. It was thought best to test the matter out by neutralizing an extract and then noting its toxicity. An injection of the same extract without neutralization served as the control. Some of the extracts used were the same as those reported in the preceding table and the same letters are used to designate them. Since the dilution in no case is above three per cent it is ignored in the volume of the neutralized extract that was injected.

TABLE IV

TOXICITY OF NEUTRALIZED CAT TISSUE EXTRACTS

TISSUE	TOXICITY			
	WHEN ACID		WHEN NEUTRAL TO LITMUS	
	C.C. INJECTED	RESULT	C.C. INJECTED	RESULT
Intestine A	4	2′	4	2′
Intestine B	4	2′	4	3′
Liver A	4	1′	4	Near death
Liver B	4	Violent shock	4	Light shock
Liver C	4	1′	4	Moderate shock
Stomach B	3	4′	4	Light shock
Brain B	4	Violent shock	4	Violent shock
Kidney B	4	12′	4	Near death
Kidney C	4	3′	4	Moderate shock
Intestine	4	2′ (clotted blood)	4	2′ (clotted blood)
Stomach	4	2′ 30″	4	5′

Apparently the acidity is not the cause of the toxicity. A careful consideration of the data in Table IV shows that the attempt to modify toxicity by adjustment of reaction failed both ways. That is, the toxicity was not appreciably lowered or raised from what it was originally.

Effect of Fatigue.—A more critical survey of the data in Table I showed that muscle tissue produced an extract that seemed to more consistently hold a high toxicity than any other one tissue. This fact caused us to consider means whereby it might be possible to radically modify the muscle tissue of an animal in its physico-chemical properties. It was proposed to extract, not only the muscle, but all other tissues of the animal and observe whether any marked change had taken place in the extract of such tissues as compared to the tissues of a normal animal. Extreme fatigue was the first to be considered. A large strong cat was selected and its urine was examined for sugar. It was found to be negative. The animal was then placed in a situation that involved a moderate but continuous muscular effort. At the end of four hours the test for sugar in the urine was strongly positive. For the next few hours the sugar remained practically constant in the urine. At the conclusion of the twenty-second hour of the exertion the urine was again negative for sugar. The presence of the sugar was used as a criterion of unusual exertion. The cat was exercised for a total of ninety hours, and then exsanguinated. The tissues were prepared and extracted as usual. Table V summarizes the injection tests of the resulting extracts.

Table V

Toxicity of Extracts from Tissues of a Strongly Fatigued Cat

Tissue	Guinea pig		C.C. injected	Result
	No.	Wt.		
Intestine	1	195 gm.	4	1′
	2	190	2	Moderate shock
Spleen	3	160	4	Light shock
Lung	4	185	4	Violent shock
Heart	5	160	4	Moderate shock
Stomach	6	190	4	3′
	7	160	3	3′
Muscle	8	195	1	Nil
	9	250	2	Light shock
	10	235	3	Moderate shock
	11	250	4	Moderate shock
	12	215	6	Violent shock
Liver	13	185	3	Light shock
	14	205	4.5	Violent shock
Brain	15	220	4	7′
Kidney	16	225	4	Nil

We have not as yet attempted to set up any standard of toxicity to which an extract might be compared. Therefore anything in the nature of an exact measure of toxicity is impossible. However, a consideration of the extracts whose toxicity is shown in Table V shows that their relative toxicity is rather less than the general average. This is especially true for the extract from muscle. More will be said about the interpretation of this data later.

Effect of Inanition.—In continuation of the attempt to modify the properties of an extract by antemortem treatment of the animal it was decided to try inanition. Two large, well-fed cats were supplied only with water. At the end of one week one cat was removed and its tissues examined.

TABLE VI

TOXICITY OF EXTRACTS FROM TISSUES OF CAT THAT HAD BEEN WITHOUT FOOD FOR SEVEN DAYS

TISSUE	GUINEA PIG		C.C. INJECTED	RESULT
	NO.	WT.		
Stomach	1	190 gm.	3	3′
	2	185	1	Violent shock
	3	180	2	5′
	4	250	1	Moderate shock
Muscle	5	170	3	Near death
	6	255	4	2′
	7	180	3	Near death
	8	185	3.5	Near death
Spleen	9	165	4	Violent shock
Heart	10	280	4	Violent shock
Kidney	11	185	4.5	Violent shock
	12	270	5	Violent shock
Lung	13	280	4	5′
	14	200	3	3′
	15	185	2	2′
Brain	16	180	4	Violent shock
	17	190	5	4′ (clot in heart)
Liver	18	250	5	Light shock
	19	170	6	6′
Intestine	20	190	5	2′
	21	195	3	3′
	22	170	2	3′
	23	175	1	3′
	24	170	0.5	Moderate shock
	25	200	1	Moderate shock

The second cat was continued in a state of inanition for a total of twenty-four days. In the course of removing the tissues it was observed that there was still some fat left under the skin and about the viscera. Due to an error in the manipulation the final extract of these tissues was made up so that each cubic centimeter represented but one gram of tissue instead of the usual two grams. If this point be kept in mind when considering the data below it will be seen that inanition has had no apparent effect on the amount of toxic material that may be extracted from the tissues of a cat.

Second Extraction of Tissue.—The residual tissue from the cat which had been without food for one week was subjected to a second extraction with alcohol. In order to increase the possibility of this extract resulting in a toxic product the tissue residues were placed in a mortar and well ground with clean sand before being placed under the alcohol for the second time. When the alcoholic extract was evaporated the small quantity of the residue was especially noticeable. In order to compensate for the evident lessened amount of material that had been extracted by the alcohol, the volume of the physiologic salt solution that was added was reduced so that each c.c. of the final extract represented 4 g. of the original tissue.

Table VII

Toxicity of Extracts from Tissues of Cat That Had Been Without Food for Twenty-four Days

Tissue	Guinea pig		C.c. injected	Result
	No.	Wt.		
Stomach	1	250 gm.	4	Light shock
	2	210	6	1 hr. 4′ (clot in heart)
	3	200	5	4′ (clot in heart)
Heart	4	220	5	Violent shock
	5	235	3.5	Moderate shock
Eye	6	210	4	Nil
Lung	7	245	5	Moderate shock
	8	285	7	Moderate shock
Kidney	9	235	6	Moderate shock
Spleen	10	225	6	Violent shock
Brain	11	220	5	Violent shock
	12	215	7	5′
Intestine	13	215	5	4′
	14	215	4	4′
	15	240	3	8′
	16	210	2	Violent shock
Liver	17	225	4	Light shock
	18	210	6	Violent shock
	19	240	7	Violent shock
Muscle	20	270	6	Violent shock
	21	305	8	Violent shock

Table VIII

Toxicity of Extract Prepared by Second Extraction of Tissue

Tissue	Guinea pig		C.c. injected	Result
	No.	Wt.		
Muscle	1	185 gm.	4.5	Violent shock
Lung	2	195	4.5	Light shock
Kidney	3	155	4	Violent shock
Intestine	4	200	2.5	Light shock
Stomach	5	180	2.5	Moderate shock

Extraction by Ether.—Instead of adding 2 c.c. of alcohol for each gram of moist tissue, ether was substituted in the same proportion. The further steps in the process were not altered from the general method outlined earlier. The tissue was left in the ether for one week. Upon evaporation of the ethereal extract the minute amount of residue foretold the probable outcome of the injection tests just as it had in the previous experiment dealing with a second extraction of tissue by alcohol.

It is evident that the toxic agent that is removable from tissue by alcohol is not extracted by ether under the same conditions. This fact coupled with a consideration of the ability of dilute alcohol to remove phosphatides from tissue marks the beginning of a line of experimentation that finally led to the conclusions of this work. A more detailed discussion of the line of thought involved will be reserved for later consideration. (See Table IX.)

Extraction of Dried Tissue.—For this experiment it was decided to use only rabbit muscle. The extracts from muscle tissue were about as free from

TABLE IX

TOXICITY OF EXTRACT PREPARED BY SUBSTITUTION OF ETHER FOR ALCOHOL IN PRIMARY EXTRACTION

TISSUE	GUINEA PIG		C.C. INJECTED	RESULT
	NO.	WT.		
Intestine	1	230 gm.	5	Nil
	2	210	9	Nil
Liver	3	190	5	Nil
	4	210	9	Nil
Muscle	5	245	9	Nil
Lung	6	195	9	Nil
Heart	7	195	7 (all)	Light shock
Kidney	8	210	9	Nil
Brain	9	200	9	Nil

technical difficulties as any, and muscle tissue could be obtained in greater quantity more readily than others. Moreover, we were becoming more thoroughly convinced that a result arrived at by the use of any one tissue could be essentially duplicated with any other. Rabbit muscle was ground finely and dried on the steam bath. By alternate grinding in a mortar and drying it was reduced to a very fine powder of uniform consistency. This dried muscle was then subjected to treatment with alcohol for five days. The quantities of alcohol and of water used in making up the final extract were based upon the weight of the moist tissue, and were not modified from the usual quantities employed.

TABLE X

TOXICITY OF ALCOHOLIC EXTRACT OF DRIED RABBIT MUSCLE

GUINEA PIG		C.C. INJECTED	RESULT
NO.	WT.		
1	230 gm.	3	Nil
2	270	4	Nil
3	280	6	Nil
4	275	10	2′
5	240	8	2′
6	275	7	2′
7	250	6	Nil

The striking thing about this data is the sharp break in the toxicity. It is noticed that any quantity above six cubic centimeters is fatal, whereas all doses below that amount are without effect. This is different from the graded effects that are usually shown by the injection of sublethal doses of extracts.

A portion of this extract was evaporated to dryness and the concentration of the solids determined. It was found to be 9.4 mg. per c.c. This is equivalent to but .4 of one per cent of the original tissue, and is less than any other like determination so far made. We will in this connection give another method for the concentration of solids that will soon be the subject of fuller discussion. The residue left in the crucible in which the extract was evaporated for the determination of the total solids was ignited to a white ash and its weight determined. It was found to represent .6 mg. per c.c. of the extract, or .03 of one per cent of the original tissue.

Inorganic Material in Tissue Extracts.—We have already given some typical figures concerning the total solids that are held in solution in the extracts of various tissues. While engaged on that point the possibility of the presence in the extracted material of a portion at least of the inorganic constituents of tissues was realized. It was but a simple matter to ignite the residue left upon evaporation of a measured portion of the extracts and note the ash left in the crucible. Strong heat was required to eliminate all carbon from the ash. It was found by several trials that ignition of the residue from 25-50 c.c. of various extracts left an appreciable ash in the crucible. In the course of some further work we will give more exact expression to the quantity of the ash.

Speculation as to the chemical constituency of such an ash was hardly necessary. In the first place it is evident that nothing could be present that had not been derived from the tissues. By reference to König's analytical work it was possible to note what the theoretical composition should be for all the tissues under examination. A part of the chlorides probably would be volatilized by the temperature of ignition, which at the same time would convert the principal element phosphorus to a pyrophosphate salt with the potassium, calcium, magnesium and other basic elements present. The ash was slowly and nearly totally soluble in water, the resulting solution being alkaline to litmus. The slight insoluble portion was at one time filtered from a solution of an ash and the volume brought back to exactly that of the original extract. A small dose of this solution was then injected into a guinea pig intravenously. A typical anaphylactic shock and death ensued. The ash in this instance had been derived from an extract of cat muscle. The amount of material in solution of the ash was found to be equivalent to 8.1 mg. per c.c. To state the same thing in another form, that is, in terms of tissue, since one c.c. of the ash solution was equivalent to 2 g. of the tissue, the inorganic ash was equivalent to 4.05 mg. per gram of tissue. Injection of 2.5 c.c. of this solution was fatal in two minutes. In the following tabulation the toxicity of the ash solutions derived from the tissues is given in comparison to the toxicity of the original extract. All the extracts were of uniform tissue value; each c.c. represented 2 g. of tissue. There was some variation in the concentration of the ash solutions derived from the extract residues. The tissue value of the ash solution of the cat muscle and of both the rabbit muscles was the same as the extract, 2 g. of tissue per c.c. The tissue value of the remaining four ash solutions was four grams per c.c. or just twice that of the others.

Consideration of the data in Table XI shows that the inorganic constituents of tissue extracts when reduced to an ash by strong ignition and then injected in water solution have a toxicity equal to in most cases and greater in some than the original extract. It is realized that the toxic agent of an ash solution can not be identical with that of the extract. There is one striking feature noted above that undoubtedly corroborates this point. It will be observed that autopsy shows that the lungs of all animals dying from an injection of ash solution are collapsed. This condition is directly opposed to the distended lungs found after death from the original extract. The contrast was very

TABLE XI

SHOWING TOXICITY OF ASH SOLUTIONS AND COMPARING THEIR TOXICITY WITH THAT OF ORIGINAL EXTRACT

ANIMAL AND TISSUE	M.L.D. OF ORIGINAL EXTRACT	ASH SOLUTION			
		GUINEA PIG		C.C. INJECTED	RESULT
		NO.	WT.		
Cat muscle	4 c.c.	1	200 gm.	2.6	Light shock
		2	180	2.3	2′ lungs collapsed
Sheep muscle	2	3	150	1	4′ lungs collapsed
		4	175	1	Near death
		5	155	1	Violent shock
		6	180	1.25	3′ lung collapsed
Veal muscle	2.5	7	160	1.5	2′ lungs collapsed
		8	210	1.5	5′ lungs collapsed
		9	200	2	2′ lungs collapsed
		10	185	1	Nil
		11	190	1.5	Moderate shock
Beef muscle	2	12	170	2	2′ lungs collapsed
		13	165	1	1′ lungs collapsed
Hog muscle	2.5	14	200	1.5	5′ lungs collapsed
		15	180	1	Nil
		16	200	1.5	Violent shock
		17	180	1.5	2′ lungs collapsed
Rabbit muscle A	3	18	260	3	Violent shock
		19	230	4	2′ lungs collapsed
Rabbit muscle B	3	20	260	3	2′ lungs collapsed
		21	215	2	2′ lungs collapsed
		22	225	1.5	Violent shock

marked. The distention on the one hand seemed to be nearly always maximum, while the collapse was apparently to the minimum. No other differences were observed upon autopsy of the animals killed by the ash solution.

The toxicity of the ash solutions turned our attention to the inorganic elements of the extracts. It was beyond reason to believe that the toxic agents of the extracts and of the ash solutions were the same. However, there is another possibility that could not be so easily disposed of. The exact condition of the inorganic material in living tissue is as yet uncertain. The probabilities are that most of it is in some sort of combination with the organic or nitrogenous portion of the tissues. Tests for acid radicals in the extracts were weakly indicative of their presence. The nature of the extracts made the interpretation of such tests precarious. So it must remain as doubtful whether the inorganic material of the extracts, acting as such, had any part in the original toxicity. This possibility is the subject of an experiment that will be reported later. However, it is not outside the realm of possibilities that the inorganic constituents in whatever combination they might have been, in the extracts, were the cause of their toxicity. This latter idea was therefore tested out experimentally.

Comparison of Alcoholic and Water Extracts.—It will be recalled that this study was evolved out of an attempt to recover Vaughan's poisonous protein cleavage product from the tissues of a cat that had been dosed enterally with the poison. Alcohol was employed as the extracting medium for two reasons. The first was the belief that the protein coagulating power of the alcohol would tend to eliminate much of the extractives of tissue. Secondly, the poison in question is more soluble in alcohol of any concentration than in

water. It was therefore expected that the differential action of the alcohol would favor its recovery from the tissue if it was present. The fact that when the absolute alcohol was added to the moist tissue it was no longer absolute was appreciated. Using the commonly accepted figures for the proportion of water in tissues and assuming an intimate intermingling of the water with the added alcohol it became about seventy-three per cent alcohol. This dilute alcohol was evidently extracting from the tissues a considerable portion of the inorganic part in whatever form it may be in the tissue. It was assumed that the inorganic material might be more soluble in water than in dilute alcohol. If this assumption should prove correct and the inorganic materials were in any manner concerned with the toxicity of the extracts, it would result in a more toxic extract. Hence it was decided to use water as the primary extracting fluid in place of the alcohol. Rabbit muscle was the tissue first subjected to such extraction. It was thought proper to make the first extraction parallel a portion of the same tissue by the alcoholic method. Then a comparison of the essential characteristics of the resulting extracts could be made. Therefore a rabbit was stripped of its muscles and they were ground as usual. The tissue was then divided into two equal parts and one was placed under alcohol, the other under water in the same proportion, 2 c.c. per gram of tissue. To the water extract formol was added to three per cent to restrain bacterial action. The final extracts are designated below as "alcohol" and "water." It is understood that the treatment of the residues left from the evaporation of the extracting liquids was identical for both and was no different from the usual method.

TABLE XII

COMPARISON OF EXTRACTS MADE FROM RABBIT MUSCLE BY ALCOHOLIC AND WATER EXTRACTIONS

	ALCOHOL				WATER			
	GUINEA PIG		C.C. INJECTED	RESULT	GUINEA PIG		C.C. INJECTED	RESULT
	NO.	WT.			NO.	WT.		
Toxicity of extracts	1	240	3	2′	1	220	3	2′
	2	255	2	Light shock	2	215	2	2′
					3	225	2	3′
					4	225	1	Light shock
Toxicity of ash solution*	1	260	3	2′	1	200	2	2′**
	2	215	2	2′	2	210	1.5	3′
	3	225	1.5	Light shock				
Concentration of solids	Total solids 33.4 mg./c.c. or 1.67% of tissue Ash 6.32 mg./c.c. Or .32% of tissue				Total solids 36.0 mg./c.c. Or 1.80% of tissue Ash 9.5 mg./c.c. Or .48% of tissue			

*Volume of ash solution equivalent to extract from which derived.
**Lungs of all animals dying from ash solution were collapsed.

Certain aspects of the above data are worthy of some consideration. It is evident that the water extraction has removed more solids from the tissue than the alcohol. The increase is 7.8 per cent. This is not a marked increase. However, the ash determination tells the real difference in the extracts. The increased quantity of inorganic material in the extract made with water is ex-

TABLE XIII

SHOWING HOW TOXICITY OF EXTRACTS CAN BE CONCENTRATED BY FREEZING

SOURCE		M.L.D. ORIGINAL EXTRACT	NO. OF FREEZINGS	GUINEA PIG		LAYER AND C.C. INJECTED	RESULT
ANIMAL	TISSUE			NO.	WT.		
Cat	Muscle	4 c.c.	1	1	190	2 top	Nil
				2	220	4 "	Light shock
				3	210	2 lower	2′
				4	225	1 "	2′
				5	220	0.5 "	Light shock
			5	6	220	4 top	Nil
				7	185	0.5 lower	Near death
				8	210	1 "	1′ 30″
Cat	Liver	5 (violent shock only)	4	9	265	4 top	Nil
				10	230	2 lower	5′
				11	220	1.5 "	Near death
				12	205	1 "	Near death
Cat	Intestine	5	4	13	210	4.5 top	Violent shock
				14	170	1 lower	1′
				15	180	1 "	4′
Rabbit	Muscle	3	5	16	210	4 top	Nil
				17	200	1 lower	2′
				18	160	0.5 "	3′
Rabbit	Liver	4.5	5	19	205	4 top	Nil
				20	170	1 lower	Near death
Rabbit	Intestine	4.5 (moderate shock only)	5	21	165	2.5 top	Nil
				22	155	1.5 lower	Violent shock
Dog	Muscle	4	1	23	210	4 top	7′
				24	220	1 lower	Violent shock
				25	160	2 "	2′ (clot)
Guinea pig	Muscle	4	3	26	185	4.5 top	Nil
				27	210	2 lower	Near death
				28	180	2.5 "	2′
Guinea pig	Liver	4.5 (near death)	3	29	190	4.5 top	Nil
				30	185	2 lower	Violent shock
				31	180	3 "	Near death
				32	220	4 "	3′
Sheep	Muscle	2	3	33	175	4 top	7′
				34	185	0.5 lower	Violent shock
				35	185	1 "	Near death
Veal	Muscle	2.5	4	36	190	4 top	Nil
				37	260	1 lower	3′
				38	185	0.75 "	Near death
Hog	Muscle	2.5	4	39	250	4 top	Nil
				40	210	1 lower	3′
				41	155	0.5 "	Violent shock
Beef	Muscle	2	3	42	240	4.5 top	3′
				43	240	2.5 "	Nil
				44	225	1 lower	2′
				45	220	0.5 "	Near death
Rabbit	Muscle	3	2	46	215	3 top	Moderate shock
				47	245	1 lower	3′
				48	250	0.75 "	Moderate shock
			5	49	185	6 top	Violent shock
				50	245	8 "	3′
				51	195	1 lower	2′
				52	215	0.5 "	2′
				53	200	0.5 "	1′
				54	190	0.25 "	Near death
				55	230	0.5 "	Near death

actly 50 per cent more than that in the regular alcoholic extract. It is also observed that the water extract has a higher toxicity than the alcoholic, which is true as well of their respective ash solutions.

Effect of Freezing.—A mixture of salt and finely cracked ice was prepared. Portions of extracts in large test tubes were plunged into such a freezing mixture and allowed to remain until frozen solidly. The tubes were withdrawn and their contents slowly thawed by standing at room temperature. The first time that this was done it was observed that the color of the extract was slightly deeper in the bottom of the extract and correspondingly faded out in the upper portion. The intermediate area was a transition zone between the conditions at the opposite ends. A slight coagulum occupied a position just above the lower, more deeply colored portion. By means of a bulb pipette with a fine bore stem it was possible to withdraw some of the bottom part without disturbing the upper layers of the tube. Withdrawal of the top portion was of course readily accomplished. A comparison of the toxicities of the top and bottom portions showed an increased toxicity of the lower more deeply colored layer and a decreased toxic effect of the top less deeply colored part. A second freezing and thawing augmented the separation into layers that had been initiated by the first freezing and made a sharper line of demarcation between the bottom layer and the coagulum immediately above it. The bottom layer after the second freezing occupied about one-fourth to one-sixth of the total depth of the fluid in the tubes. Repeated freezing and thawing continued the layering process until the upper one-third to one-half of the fluid was nearly water white. The most of the color was concentrated in the bottom layer. The transition zone became lessened in extent necessarily. It was no longer a true transition zone excepting upwards. The break between the lower part and the coagulum area was sharp. This maximum effect could be obtained by five or six freezings and thawings. A larger number did not carry the effect any farther. In fact it could not be carried to a better separation on account of the diffusion that went on simultaneously with the thawing of the ice.

All the extracts in Table XIII were prepared by the use of alcohol as the primary extracting fluid. The last tissue in Table XIII is the extract of rabbit muscle prepared alongside the extraction of another portion of the same muscle by water. The data concerning this extract were given in Table XII. The freezing process was applied to the water extract, it being repeated four times. The separation into an upper watery layer and a lower colored layer was remarkably complete and sharp. Further, there was no coagulum anywhere in the tube. The injection tests gave the results as shown in Table XIV.

Table XIV

Result of Freezing an Extract of Rabbit Muscle Prepared by Use of Water Only

Guinea pig		Layer and c.c. injected	Result
No.	Wt.		
1	240	4 top	Nil
2	270	6 "	Nil
3	230	1 lower	2′
4	225	0.5 "	3′
5	200	0.25 "	2′

Portions of the top and lower layers of this extract were subjected to a determination of their solids and ash by the usual methods of evaporation and ignition. The resulting values were found to be:

	TOP LAYER	BOTTOM LAYER
Total solids	3.5 mg./c.c.	180.4 mg./c.c.
Ash	0.9 mg./c.c.	46.7 mg./c.c.

The ash resulting from the treatment of the bottom portion was taken up in water and the insoluble part filtered out. The volume was adjusted to twice that of the extract represented, so that each c.c. was equivalent to one gram of tissue. Injection of 0.5 c.c. of this ash solution was fatal to a 200 g. guinea pig in two minutes. The lungs were collapsed. It might be of some interest to give the figures showing how the solids in solution were concentrated in the lower layer for one more extract. The extract in question is the last one in Table XIII, made from rabbit muscle.

TABLE XV

SHOWING THE EFFECT OF FREEZING ON THE DISTRIBUTION OF SOLIDS IN RABBIT MUSCLE EXTRACT

	TOTAL SOLIDS	ASH
Homogeneous extract	30.67 mg./c.c.	5.64 mg./c.c.
Lower layer after two freezings	73.84 " "	14.4 " "
Lower layer after five freezings	118.6 " "	26.6 " "
Top layer after five freezings	7.35 " "	1.35 " "

The figures for the solids and ash after the five freezings would undoubtedly have been much greater had not the withdrawals of a small portion of both top and bottom layers been made for injection and determination of solids and ash after the second freezing. However, the trend of the solids to move to the bottom is well shown by the figures as they stand.

Effect of Dialysis.—If there should be two toxic substances in the extracts it was thought they might possibly be separated by dialysis. An extract of rabbit muscle was prepared, using alcohol as the extracting liquid. The final extract was made up with distilled water. Parenthetically, we may remark that this extract demonstrates that nothing is gained by a long continuation of the primary extraction period. In this case the tissues were left under the alcohol four weeks, yet the toxicity was no greater than if left for but two days as was done in some instances. Three c.c. killed in two minutes; 2 c.c. resulting in a violent shock only.

Collodion sacs were prepared by the Novy method and mounted on cut off test tubes of appropriate size. In each case the sacs were tested for leaks before using. They were then filled with the extract to the glass line. This point furnished a convenient mark from which to note and, if desired, to measure the endosmosis. The amount of endosmosis could be accurately determined by difference between the volume of the extract placed in the dialyzer and the volume of water required to fill the sac to the liquid line at the conclusion of the

dialysis. For the first dialysis 40 c.c. of extract was used, and was continued for 24 hours at room temperature against distilled water running so that one could count the drops as they fell from the overflow. Endosmosis was 5 c.c. The increase is ignored in all volumes and figures for concentration of solids. The toxicity of the dialyzed extract was the first point to claim attention.

Table XVI

Toxicity of Dialyzed Extract of Rabbit Muscle

Guinea pig		c.c. injected	Result
No.	Wt.		
1	195	3	Nil
2	190	5	Moderate shock
3	200	8	3′
4	190	6	Light shock

As the M.L.D. of the undialyzed extract was 3 c.c. it is evident that the toxicity has materially decreased. In looking for an explanation of this, the fate of the solids in solution was determined. Measured portions of the dialyzed and undialyzed extracts were subjected to the usual process of evaporation and ignition.

Table XVII

Effect of Dialysis on Concentration of Solids

	Total solids	Ash
Undialyzed extract	30.67 mg./c.c.	5.64 mg./c.c.
Dialyzed extract	5.8 " "	0.4 " "

The results of this experiment pointed clearly to a close relationship between the toxicity of an extract and the solids held in solution. The fact that the material in solution did in large part dialyze out so readily settled its status in the extract. It was at one time thought that the solids might be in a colloidal solution, or possibly in a larger suspension or emulsion. Inability to remove any appreciable amount of material by high speed centrifugation, accompanied by an unaltered toxicity, made the notion of a suspension or emulsion no longer tenable. The only conclusion left, that of a true solution, is made much more plausible by the results of dialysis.

However, we were no nearer the truth concerning the possibility of two substances in the extract than before. It was decided to continue the investigation of this point by varying the conditions of the dialysis or the permeability of the sacs. The following protocols give the details involved:

(a) Rabbit muscle was extracted with alcohol and made up with distilled water. The toxicity of the original homogeneous extract was:

Guinea pig		c.c. injected	Result
No.	Wt.		
1	225	3	1′ 30″
2	250	2	Near death

A very thin sac was prepared and a portion dialyzed for seven hours. The endosmosis was very marked and required a factor of .812 to be applied to the final volume in order for it to become comparable to the original extract. This correction is made in the volumes in the injection tests that are here reported for the dialyzed extract.

Toxicity of Extract Dialyzed Seven Hours

GUINEA PIG		C.C. INJECTED	RESULT
NO.	WT.		
1	220	2.4	Nil
2	245	3.2	Nil
3	225	4.9	Light shock
4	265	5.7	Moderate shock

The values for the solids and ash in the dialyzed and undialyzed extracts were found to be:

	TOTAL SOLIDS	ASH
Undialyzed extract	33.0 mg./c.c.	6.34 mg./c.c.
Dialyzed extract (7 hrs.)	9.3 " "	1.04 " "

Another portion of this extract was dialyzed for twenty-four hours in an ordinary sac. The endosmosis was slight and was ignored. An injection of six and eight cubic centimeters into two guinea pigs of 200 g. was devoid of toxic effect. No determination of solids was made on this latter portion.

(b) Another extract of rabbit muscle was prepared by alcoholic extraction. Three c.c. killed a guinea pig in two minutes. A dialyzing sac was made and mounted and then permitted to become air dry by standing at room temperature. The effect on the sac is to markedly lessen its permeability. The dried sac was then filled and placed in a bath at 45° C. for two hours. No endosmosis had taken place in this time. Three c.c. were withdrawn and upon injection killed the animal in two minutes. The dialysis was discontinued, as it was evident that the sac was so impermeable that no results could be expected.

(c) Another sac of moderate thickness was prepared, and when filled with the extract was placed in a bath that was adjusted to a temperature of 50°-55° C. The dialysis was continued for two hours. The endosmosis was quite marked, amounting to 20 per cent of the original volume. This is ignored in the injection tests and figures for solids and ash determinations.

Toxicity of Extract Dialyzed Two Hours at 50-55° C.

GUINEA PIG		C.C. INJECTED	RESULT
NO.	WT.		
1	205	3	Nil
2	280	6	5′
3	275	5	Nil
4	290	6	Nil

The determination of solids and ash gave the following results:

	TOTAL SOLIDS	ASH
Undialyzed extract	33.4 mg./c.c.	6.32 mg./c.c.
Dialyzed extract	4.95 " "	Nil

It is to be observed that the figures for both the total solids and the ash in the undialyzed extracts reported above in "a" and "c" are quite close together. These extracts were made from the tissue of different rabbits on separate occasions. Such agreement as this is at least indicative of a possibility of the preparation of a consistent extract by following closely the same technic. As far as these dialysis experiments are concerned, it is apparently impossible to make any separation of the constituents of an extract by differential dialysis.

Effect of Boiling Extracts.—On three occasions a muscle extract was boiled to observe whether there was any alteration of its toxicity. The first time an extract of cat muscle was actively boiled in a large test tube over an open flame for five minutes. A fine coagulum was formed in the extract. The boiled extract was divided into two portions and one was filtered. Then injections were made of both the filtered and the unfiltered boiled extract. As a control, injection of unboiled extract was made. No differences could be detected in the effects of the three portions.

The next extract that was boiled was also from cat muscle. It had a slight opacity. Boiling one minute caused this to disappear. No coagulum was formed in this extract. Cooling under the tap did not restore the opaque appearance of the extract. No change in toxicity could be noted. Finally an extract of rabbit muscle was boiled five minutes. A coagulum similar to that produced in the extract of cat muscle made its appearance. The boiled extract was injected both filtered and unfiltered. No differences could be observed between these two portions and an unboiled portion. We believe that these tests warrant the assertion that boiling has no effect on the toxicity of a muscle extract.

Filtration of Muscle Extract Through a Berkefeld.—An extract of rabbit muscle was prepared with water as the primary medium of extraction. A portion was then passed through a Berkefeld "N" filter. As far as appearances were concerned the extract came through unaltered. Table XVIII shows that the toxicity remained constant also.

TABLE XVIII

FILTERING RABBIT MUSCLE EXTRACT THROUGH A BERKEFELD

GUINEA PIG		C.C. INJECTED	RESULT
NO.	WT.		
1	170	1 filtered	Nil
2	170	1 "	Violent shock
3	160	1.5 "	3′
4	170	1.5 "	3′
5	165	1 unfiltered	Violent shock
6	170	1.5 "	3″

The high toxicity of this extract may be noted. It was prepared by the use of water as the primary medium of extraction. We have already cited the experimental data showing the essential differences between an alcoholic and a watery extraction. This extract substantiates our contentions then made concerning extracts made with water.

Phosphates and Neutrality.—Inasmuch as we wished to do some work on the inorganic ash it was decided to prepare a reasonably large quantity of it. Therefore 966 g. of rabbit muscle was extracted with water and the final extract made up with distilled water to 483 c.c. No test of the toxicity was made, but it was all evaporated and the residue ignited. The resulting ash was taken up in the same volume of water and the insoluble portion filtered out. This

ash solution was evaporated to dryness and the residue was scraped together, carefully ground in a mortar, dried and weighed. The product thus obtained represented the water soluble portion of the inorganic ash, that had been extracted from the rabbit muscle (960 gms.) by water. It was found to weigh 4.54 g. This was equivalent to 4.7 mg. of ash from each gram of the moist tissue. The concentration, therefore, in the water solution was 9.4 mg. per c.c. Or the ash was 0.47 of one per cent of the tissue. A one per cent solution of this ash was made up. This solution was nearly of the same concentration as the original solution of the ash when the whole quantity was in 483 c.c. of water. Calculation shows that solution to have been .94 of one per cent. The one per cent solution was perfectly clear and water white. It was alkaline to litmus and phenolphthalein. One c.c. injected intravenously into a guinea pig was fatal in four minutes. Twenty-five c.c. of this one per cent solution required .25 c.c. of normal succinic acid to discharge the pink color of the one drop of phenolphthalein indicator that had been added. The toxicity of the neutralized solution was unaltered. Portions of the solution were also carefully neutralized with acetic, hydrochloric, and sulphuric acids. In each instance the toxicity remained unchanged.

The application of qualitative chemical tests to the solution of the ash showed the presence of chloride and sulphate radicals in rather minute amounts. By the use of differential tests the pyrophosphate radical was shown to be present in considerable quantity. An attempt was made to precipitate out the pyrophosphate radical by careful titration with silver nitrate. Two methods of determining the end point were employed. One, and the most successful, was to let the precipitate settle and then carefully add another drop of the reagent, noting whether a precipitate formed at the point where it was added. The other method used was that of potassium chromate as an indicator of free silver ions. A drop of the ash solution that was being precipitated by the silver nitrate was added to a drop of chromate indicator and the presence or absence of silver chromate noted. When the end point was reached the solution was allowed to stand for some time for the precipitate to settle out. Then a few c.c. of the supernatant liquid was withdrawn by a bulb pipette. Injection of this into guinea pigs showed that the toxicity had been reduced about one-half. That is, where the M. L. D. of the original ash solution was one c.c., after precipitation 2 c.c. could be injected and one-half of the pigs lived. All animals receiving injection of the precipitated ash solution showed a shock of some severity. Not a great deal of reliance can be placed on this experiment. It was shown by appropriate controls that the slightest excess of silver nitrate would produce death. In attempting to titrate to an end point in which the presence of the added ion in an unbound condition was used as the indicator it was practically certain that sufficient of these silver ions were present to upset any rigid interpretations of the injection of such a treated ash solution. However, it is significant at least that when the pyrophosphate was precipitated the toxicity showed some decrease.

The same experiment was tried with barium chloride as a precipitant, but with less success.

The phosphorous in the ash solution was determined by a standard volumetric method. It is not necessary to give the details of the procedure, since they were the same as would be employed by anyone for the same purpose and are in any standard textbook of volumetric analysis. It was determined that the ash contained phosphorus, calculated as phosphorus pentoxide to the extent of 34.83 per cent. Extending the significance of this value, it means that injection of 3.48 mg. phosphorus pentoxide, when in the form of pyrophosphate radical, is fatal to a guinea pig.

Toxicity of Pure Phosphate Salts.—It was decided to test the very obvious indication just brought out concerning the toxicity of pyrophosphate radical by the use of pure salts. For these tests Kahlbaum's salts were employed. However, due to the uncertainty of hydration in phosphate salts, uniform solutions were employed, and analytical results relied upon for information concerning the exact quantity of material in solution. The data will be given in form of protocols.

SODIUM ORTHO-PHOSPHATE

A one per cent solution was prepared. It was alkaline to litmus and phenolphthalein. Injection of this solution gave the following results:

GUINEA PIG		C.C. INJECTED	RESULT
NO.	WT.		
1	170	1	Nil
2	190	4.5	Nil

Twenty-five c.c. of the solution required .7 c.c. of normal succinic acid to neutralize to phenolphthalein. Injection of 4.5 c.c. of the neutralized solution was still entirely without effect. Volumetric analysis showed phosphorus calculated as phosphorus pentoxide to be 24.9 per cent. Therefore, 11.2 mg. of phosphorus pentoxide, when in the form of orthophosphate radical is without any effect upon injection into guinea pigs.

SODIUM METAPHOSPHATE

A one per cent solution was made up. It was acid to litmus and phenolphthalein. The injection tests resulted as follows:

GUINEA PIG		C.C. INJECTED	RESULT
NO.	WT.		
1	180	1	3′
2	170	0.5	Moderate shock
3	185	0.75	3′
4	165	0.75	2′ 30″
5	185	0.5	Light shock

Twenty-five c.c. of this solution required .33 c.c. of normal sodium hydroxide solution to neutralize to phenolphthalein. The injection of the neutralized solution gave the following results:

GUINEA PIG		C.C. INJECTED	RESULT
NO.	WT.		
1	170	1	2′
2	150	0.75	Violent shock
3	150	0.75	Violent shock; dead in 12 hours
4	150	1	Violent shock; dead in 12 hours
5	205	1	Violent shock; slow recovery
6	215	1.25	2′

Volumetric analysis showed the presence of 57.48 per cent of phosphorus as phosphorus pentoxide. Hence for unneutralized solutions of sodium metaphosphate, 4.32 mg. phosphorus as the metaphosphate radical is fatal for the guinea pig. When the solution is made neutral to phenolphthalein the amount is increased to 7.18 mg.

SODIUM PYROPHOSPHATE

In order to make more certain that the salt was all in the form of pyrophosphate it was strongly ignited before using. A one per cent solution was employed as before. The solution was alkaline to litmus and phenolphthalein. Injection of this solution gave the following results:

GUINEA PIG		C.C. INJECTED	RESULT
NO.	WT.		
1	185	1	2′
2	200	0.5	2′
3	180	0.25	Light shock
4	235	0.5	Violent shock
5	225	0.5	10′

The one per cent solution was diluted with distilled water volume for volume, thus making it a .5 per cent solution. Injection of the diluted solution resulted as below:

GUINEA PIG		C.C. INJECTED	RESULT
NO.	WT.		
1	205	1	3′
2	195	0.5	Nil
3	215	1	3′

Twenty-five c.c. of the one per cent solution required .5 c.c. of normal succinic acid for neutralization to phenolphthalein. Injection of the neutralized solution showed that the toxicity was the same as before. Volumetric analysis gave 52.85 as the value for phosphorus calculated as phosphorus pentoxide. The theoretic amount for a pyrophosphate salt is 52.97 per cent. Therefore, 2.64 mg. of phosphorus pentoxide in the form of a pure pyrophosphate salt is fatal for a guinea pig. Neutralization of the solution does not alter the toxicity.

The lungs of all animals dying from an injection of any of the sodium salts or the salts recovered from the extract were collapsed, and pink in color. The blood was in all cases fluid, the heart in one timed instance continuing to beat for one hour and forty-five minutes. The parallel between the toxicity of the pyrophosphate salt and the salts from the extract is the outstanding feature of this experiment. It seems sufficiently established by this test that the toxicity of the ash from the extracts is due to their content of potassium pyrophosphate.

Toxicity of Rabbit Muscle Extract for Rabbits.—An extract of rabbit

muscle with an M.L.D. of 1.5 c.c. for 200 g. guinea pigs was prepared by the use of water only. Some half grown and baby rabbits being available it was decided to make a few injections of this extract and note its toxicity for the homologous animal.

TABLE XIX

TOXICITY OF RABBIT MUSCLE EXTRACT FOR THE HOMOLOGOUS ANIMAL

RABBIT		C.C. INJECTED	RESULT
NO.	WT.		
1	280	2.1	Nil
2	275	4.2	1′ 30″
3	1085	8.2	Nil
4	1290	20.0	2′

In the tests in Table XIX rabbits number one and three received an injection that was fatal for guinea pig per kilogram of weight. Rabbits number two and four received twice the fatal quantity for guinea pigs per kilogram of weight.

Experiments with Serum.—On several occasions during the progress of the experimental part of this work an attempt was made to modify the toxicity of extracts, by the addition of rabbit serum and guinea pig serum. As far as the use of the serum of normal animals is concerned we are prepared to state that it is entirely without effect.

By repeated small injections an attempt was made to immunize rabbits against rabbit muscle extract. The injections were one-tenth the fatal quantity per kilogram of guinea pig, calculated on the weight of the rabbits. The injections were made every other day in the ear veins. On the third injection one of the rabbits gave the typical cry of an anaphylactic rabbit and was dead in two minutes. A second rabbit died on the fifth injection, notwithstanding a reduction of the dose to one-half the amount used in the beginning. The third rabbit successfully received six injections, but lost one hundred grams in weight. The animal was kept one week after the last injection and the serum secured by the usual process of bleeding in a pipette, rod defibrination, followed by immediate whirling out of the cells. This serum, possibly containing antibodies against the extract, was then added to one M.L.D. of the same extract that had been injected into the animal, and the resulting mixture tested on guinea pigs. The results of the injections are given in Table XX. Another series of mixtures of the serum and extract was prepared and then incubated at 37° C. for one hour. Following the incubation, the tubes stood at room temperature for fifteen hours and then the injections were made. The data is in Table XXI.

It is seen that the effect of the serum is nothing more than that of dilution, for the same slight evidences of weakening of toxicity can be produced by the use of physiologic salt solution. The attempt to immunize the rabbits also shows that the effect of repeated small injections apparently becomes cumulative. However one may try to explain the deaths of the rabbits, the fact remains that they were killed by a total quantity of extract that amounts to .3

TABLE XX

TOXICITY OF RABBIT MUSCLE EXTRACT WHEN MIXED WITH SERUM OF A RABBIT THAT HAS BEEN SUPPOSEDLY IMMUNIZED

GUINEA PIG		C.C. EXTRACT	C.C. SERUM	C.C. PHYSIOLOGICAL SALT	RESULT
NO.	WT.				
1	190	1.5	0.5	0	5′
2	185	1.5	0.5	0	3′
3	225	1.5	1.0	0	Violent shock
4	205	1.5	1.0	0	6′
5	215	1.5	1.5	0	Violent shock
6	210	1.5	1.5	0	10′
*7	250	1.5	0	1.5	Violent shock
*8	200	1.5	0	1.5	2′
*9	215	1.5	0	0	3′

*Controls.

TABLE XXI

TOXICITY OF RABBIT MUSCLE EXTRACT WHEN INCUBATED WITH SERUM OF SUPPOSEDLY IMMUNIZED RABBIT FOR ONE HOUR; ROOM TEMPERATURE FIFTEEN HOURS

GUINEA PIG		C.C. EXTRACT	C.C. SERUM	C.C. PHYSIOLOGICAL SALT	RESULT
NO.	WT.				
1	250	1.5	0.5	0	Violent shock
2	200	1.5	0.5	0	3′
3	205	1.5	1.0	0	Violent shock
4	210	1.5	1.0	0	5′
5	200	1.5	1.5	0	3′
6	200	1.5	1.5	0	Violent shock
7	200	1.5	2.0	0	Violent shock
8	180	1.5	2.0	0	Violent shock
*9	200	1.5	0	1.5	5′
*10	245	1.5	0	1.5	Violent shock
*11	250	1.5	0	2.0	Near death
*12	220	1.5	0	2.0	Violent shock
*13	200	1.5	0	0	3′
*14	210	1.5	0	0	5′

*Controls.

in one case and .5 in the other of the quantity that would have been required to have killed them in one single injection on the assumption that rabbits are as susceptible as guinea pigs.

DISCUSSION

The first or historical part of this paper requires but little further consideration. The reading of it has no doubt left the impression that there is yet considerable confusion in the field of organ extracts. Direct contradiction prevails on some points and agreement on certain others; but by far the larger number of questions involved are still in the balance. The one question that all have striven to answer, directly or indirectly, is the identity of the toxic agent in organ extracts.

To reflect for just a moment on the lack of agreement among the workers in this field. By a more careful reading of the details of their work one can see a plausible reason why such variant conclusions have been reached. When

one takes into consideration the diversity of workers, and hence of technic, the wide range of materials that have been examined, and the variety of animals that have been used as recipients upon which to test toxicity, it is seen at once that sharp conflicts of opinion are inevitable. Probably the variation in the technic of extraction, together with the use of different animals as recipients are the most potent factors in this matter. The latter point we believe to have especial significance. If the guinea pig may be said to be too sensitive in its response to injections, the converse is probably true of all other laboratory animals, and especially of the rabbit, which has been used so extensively in organ extract work. To illustrate, if one injects a series of half a dozen guinea pigs with graduated doses of some toxic substance, within limits, all give some definite response to the injections. The gap between no response and an easily observable effect will be relatively small in terms of dosage. This is not so for the rabbit. They receive with equanimity relatively large doses of toxic material, even bordering on the fatal quantity. Thus it is seen how two independent operators could easily arrive at opposite conclusions. One by injecting doses into rabbits that were just under the M.L.D. would get only negative results; the other by use of a quantity but slightly larger, yet over the fatal amount, makes a positive observation. Both are correct in their observations, yet the published work seems absolutely contradictory at first reading. Our personal experience with rabbits strongly corroborates this possible explanation of some of the confusion in the literature of organ extracts.

The statement made earlier concerning the circumstances under which this study was initiated may be recalled. The extraction process that was then employed is admittedly a crude procedure. However, it resulted in a toxic extract from the tissues of a normal cat. It was the substance that was in that extract that we wished to know more about, therefore the technic by which it was obtained has been quite closely followed throughout this work. It can be readily understood, that in extracting such a complex material as tissue, that any radical change in method would result in a corresponding change in the extract. The attempt to extract the tissue with ether in place of the alcohol well illustrates the point. Or, the previous drying of the tissue, followed by alcoholic extraction, which produced an extract of such negligible toxicity. The lessened toxicity of the extract from the tissues of the fatigued cat is not so readily explained. Various factors were influencing the cells of that animal during the period of fatigue, whereby they could have been markedly modified. The exertion, lack of food, worry, and the necessity of metabolism of something as a source of energy, is a combination that has many possibilities of altering an organism. The experiment on inanition alone rules out that factor, as the cat subjected to that test showed no effects of the treatment in the resulting extract of its tissues. Without going into the theoretical aspects of the matter, it may be said that authorities are agreed that two changes would ensue in the fatigued animal. One would be a change of cell contents; a transfer of energy producing material from certain cells to others more vitally concerned with the maintenance of life, such as the heart and nervous tissues. From the

viewpoint of our purposes, the change that probably took place in the cell membranes was the more potent. This assumes of course that the toxic agent of organ extracts is a constituent of cells, and must of necessity be removed through the membranes in extraction. Even if there was no change whatever in the cell contents, the decreased permeability of the membranes is very likely. This is shown by the failure of the extraction process to remove anywhere near the usual amount of toxic substance from the tissues, judging by the results of the injections.

Up to the time when water was employed as the extracting medium the extraction process had not been aimed at any particular substance. It has already been explained how our efforts of extraction became more concerned with the inorganic constituents of the tissues. The primary extraction with water resulted in an enormous increase in the bulk of the extractives removed from the tissue. However, by carrying the evaporation of the water to absolute dryness, much of this material was so changed that it was not taken up by the next treatment with the water. The data shows the actual increase of total solids to only be about eight per cent over that contained in the extract prepared by the use of alcohol as the primary extracting liquid. The increase in the inorganic matter as determined by the ignition was approximately fifty per cent. The size of dose required to kill was reduced in the case of rabbit muscle to about one-half what it had been when alcohol was used for the extraction. It would seem that the connection between the inorganic part of the extracts, in whatever form they may be, and the toxicity is close enough to warrant the belief that the toxicity is caused by this part of the material in solution. The exact form in which the inorganic material was disposed is an unsettled question. Undoubtedly some small part of it is free inorganic salts. It was found impossible to separate the inorganic from the organic substance except by ignition. Dialysis might have accomplished this result but failed to do so. This points very strongly to the probability that the inorganic elements were in combination with something else. The matter can be considered from the standpoint of the principal radical present most advantageously. As has been shown the acid radical most abundant in the ash is the phosphorus. When one considers the possible forms of combination of phosphorus in the animal body, the so-called "phosphatides," in relation to the method of extracting the tissues, it will be seen that lecithin is the most probable combination that fits the circumstances of the extraction. Further the widespread distribution of lecithin and the extractable poison would support such a view. However, lecithin is said not to dialyze. Even its solution in water is somewhat dubious. These statements are made for reasonably pure lecithin, and it is certain that we are not working with a pure specimen of anything, whatever its identity may be. All laws of solubility and behavior of substances in solution are based on data from the behavior of the pure substance. When two or more substances, even when chemically pure, are present in a solution, the result of their status is not conformable to any fixed rule for either alone. The condition when such a complex as organ extracts are placed in water would not be the most simple. This

it is believed explains the situation with respect to our tissue extracts. Disregarding entirely what the toxic agent may be, the complexity of the material is sufficient to rule out any rigid statement concerning solubility, dialysis, or other phenomena of any one substance that may be present. One fact can not be escaped. That is that in the most toxic extracts, analysis showed over one-half of the inorganic constituents of the tissue to be present, and the toxicity rose as the ash value of the extract was increased.

Early in this work we had concluded that the toxic agent of tissue extracts was some stable substance. Anything in the nature of a ferment was excluded by the method of preparation of the extract. In the first place alcohol was used to extract the tissue; ferments are not able to withstand the concentration to which they would have been subjected. Further, some rabbit livers had been saved from time to time as the animals had been used for other purposes. They were preserved by dropping into a large bottle containing absolute alcohol at the start. The most recent of these livers had been in the alcohol for about one year. They were ground and the required amount of water added to the alcohol in which they had been kept to make the volume up to the usual 2 c.c. per gram of tissue. The final extract proved to be the most toxic for liver ever prepared; 1.5 c.c. proving fatal. Secondly, the alcoholic or water extraction liquid was heated during its evaporation, which was carried to relative dryness when alcohol was used and to positive dryness in the case of water, to a higher temperature than ferments can withstand. Then, the extracts themselves were stable on boiling. The extracts showed no deterioration on standing, either at room temperature or in the ice box. Extracts thus kept for three months showed no decrease in toxicity. Whenever an extract was kept for any length of time, it was preserved from bacterial activity by a few drops of trikresol.

The work upon the toxicity of the pure phosphate salts was for the purpose of confirming a well grounded notion as to the toxic agent in the inorganic salts derived from the extract by ignition. Gamgee, Priestly, and Larmuth[36] had noted the differences in the effects of the three forms of phosphoric acid as early as 1877, and had made a special study of the influence of the pyrophosphate salt on heart and circulation. They used rabbits and frogs, and made their injections subcutaneously and intravenously. Gardner and Symes[37] repeated their work in 1910, and confirmed the same. They ascribed the effects of the phosphoric salts to their alkalinity. Starkenstein[34] made a more minute investigation of the effects of the various acid radicals, that it is possible to obtain with the phosphoric acids, due to their polyvalency, and was also led to believe that the alkalinity of the pyrophosphate salts was responsible for their marked activity. Crawford[38] after investigating the ill results of feeding cottonseed meal concluded that the pyrophosphates produced by the method of manufacture were the cause of the deleterious effects. Thus we see that there is ample evidence that the phosphate salts, and especially the pyrophosphates are very toxic substances when introduced into the body by any channel. König[39] states that phosphoric anhydride constitutes from 36 to 48 per cent of the mineral part of

various forms of flesh. The salt that we prepared and subjected to analysis contained 34.8 per cent of phosphoric anhydride. It was necessarily in the pyrophosphate form by reason of the method of its preparation, and was undoubtedly the cause of death in animals injected with a water solution of the salts. The collapsed condition of the lungs of animals dying from injections of either pure phosphate salts or of the salts from the tissue extracts, was a very constant feature. If the statement is acceptable that an anaphylactized animal dies because air can not get out of the lungs, because of the constricted bronchioles, then it would be logical to believe that these animals died because air could not get into the lungs. The dyspnea was very marked, indicating a condition of air hunger exactly analogous to that of animals injected with organ extracts or anaphylatoxin.

The method of preparing the extracts would result in a low protein content. In fact, no satisfactory test for protein was ever made on an extract. The biuret test was negative. In view of the small amount of protein, if any, that was in the extracts, the attempt to immunize rabbits was inevitably doomed to not succeed. The toxic agent of the extracts we believe to have shown to be a chemical entity, and to act as such in the animal body. However, its apparent cumulative effects on repeated injection might be interpreted as a state of sensitization.

SUMMARY AND CONCLUSIONS

The tissues of seven species of animals were extracted with alcohol and found to yield a toxic extract. We believe that the tissue of all animals if similarly extracted would likewise produce a toxic extract.

It was found that the extract of the tissues of the cat, which may be considered representative of all other tissues, contained solids in solution varying from .47 to 1.83 per cent of the original tissue.

The extracts were acid in reaction with the occasional exception of the extract of stomach and intestine. Adjustment of the reaction to neutrality did not alter the toxicity of the extracts.

There was some evidence that toxicity of the extracts could be modified by previous treatment of the animals, especially by fatigue. Inanition was without effect.

Ether does not extract the toxic substance from tissue.

Drying and fine division of rabbit muscle followed by alcoholic extraction gave an extract of negligible toxicity. In view of statements that are to follow, we do not believe that the toxic agent was destroyed by the drying, but rather that it was rendered insoluble in absolute alcohol.

Ignition to a white ash of the solids in extracts prepared by the use of alcohol, shows an inorganic residue of approximately .4 per cent of the tissue. Subsequent solution of this ash to the volume of the extract from which it was obtained, followed by injection, shows it to be always equally toxic, and in some cases more so, than the extract from which it was derived.

It was found that water could be substituted for alcohol as the primary extracting medium, and that a more toxic extract resulted. Further investiga-

tion of this extract showed that the total solids had been increased by the use of water about 8 per cent, and the inorganic residue by 50 per cent.

The increase in toxicity of the water extracts, as measured in terms of reduction of size of dose required to kill, was approximately parallel to the increase of the inorganic material in the extracts. We, therefore, believe that the inorganic constituents of the extracts, in whatever form they may be, are responsible for the toxicity of the extracts.

That the inorganic substances were in some sort of combination is indicated by the failure of dialysis to make any separation of organic and inorganic materials. Whatever is in the extracts dialyzed freely.

By repeated freezing and thawing the toxic portion of the extracts could be concentrated to a very small volume in the lower part of the container in which the extracts were frozen. Five or six freezings gave the maximum effect. The increase in toxicity of the lower concentrated portion was roughly equivalent to the increase of solids in solution. The lack of toxicity in the uppermost portion of such a frozen extract was almost absolute.

Boiling does not affect the toxicity of muscle extracts.

The toxic agent of muscle extracts is not removed by passage through a Berkefeld N filter.

Pyrophosphate salts are highly toxic for guinea pigs upon intravenous injection. By comparative tests between pure phosphate salts and the inorganic salts derived from the extract by ignition, it was shown that the toxicity of the ash solutions was caused by their content of pyrophosphates.

The toxicity of rabbit muscle extract could not be modified by treatment with serum, either with or without incubation. This statement applies to both serum from a normal animal and serum from an animal that had been repeatedly injected with the extract, and might therefore have been immunized against the extract.

Rabbit muscle extract is toxic for rabbits, but in a higher proportion per kilogram of weight than for guinea pigs.

The attempt to immunize rabbits by successive small injections of extract shows that the effects of the extract by this manner of injection become cumulative and are exaggerated beyond what would have been produced by a single injection of the total dosage up to the time when the animal succumbs. Lack of protein material in the extracts forbids the use of the term "sensitization" as ordinarily understood. Yet the whole phenomena is typical of such a state.

The general trend of the experimental part of this work indicates that the toxic agent in tissue extracts is a stable chemical entity or entities. We believe that the evidence is sufficient to warrant the statement that the inorganic materials of the extracts, *especially the phosphorus*, in whatever form they may be are the toxic agents of tissue extracts.

ACKNOWLEDGMENTS

I wish at this time to express my thanks to Dr. V. C. Vaughan for his kind suggestions and advice, and for his friendly interest in the progress of this

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PHYSIOLOGIC CHANGES PRODUCED BY VARIATIONS IN LUNG DISTENTION*

A Body Plethysmograph and Its Application to the Study of Lung Distention in Relation to Circulatory Phenomena

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IN the course of investigations including a study of the circulatory changes due to distention and collapse of the lungs, of the nervous mechanism of respiration, and of the pathologic effects of overdistention it became necessary to devise apparatus by means of which accurate records of changes in lung volume could be obtained under conditions of normal or artificial respiration. It was essential that any degree of lung distention or collapse could be maintained for a considerable length of time by methods causing changes in the intrapulmonic and intrathoracic pressures approximating as nearly as possible those occurring during natural respiration. It was also desired that the apparatus should be capable of producing rapid and rhythmic changes in lung volume while a constant mean degree of distention was maintained. It was further necessary that provision be made for recording blood pressures, stimulating or freezing nerves, injecting solutions and other procedures.

The special and excellent lung plethysmographs designed either by Cloetta[1] or by Jackson[2] did not meet the requirements of our investigations which were, however, fulfilled by an adaptation of the earlier method of Bernstein[3] which consisted in placing the animal in a hermetically sealed plethysmograph, connecting the trachea with the outside air, and recording changes in lung volume from the displacement of the plethysmographic air. Certain objectionable features of this older method are, we believe, eliminated in the apparatus which we have devised and described below, while additions have been made which render it adaptable to a much wider range of experimental work. Description is facilitated by reference to two photographs (Figs. 1 and 2) and a detailed drawing (Fig. 3).

The plethysmograph** is a wooden box with a plate-glass cover. It is constructed to accommodate a medium sized dog, and leave the minimum amount of interior air space. The sides, ends, and bottom of the box are made of two layers of wood glued together with the corners lapped and fastened with screws to render it air-tight and to prevent warping. Leaks are further guarded against by a heavy inside coating of shellac and hard paraffin. The upper edges of the sides and ends of the box are surmounted by a broad wooden flange upon which the glass cover rests. In earlier attempts to secure a tightly fitting cover, the flange was in turn surmounted by a plate glass rim embedded in plaster of Paris. Leakage between the plaster of Paris and the glass rim frequently occurred, and the glass rim was abandoned for a simplified construction in which the wooden flange was carefully trued to the surface of the plate-glass cover. An air-tight union for such pressures as our animals have been subjected to, was secured by coating the

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**The plethysmograph was made by Mr. Tudor T. Hall, mechanician for Tulane University.

flange with heavy machine oil† before placing the glass cover in position.

For convenience, operative work in preparation for an experiment is performed on a special dog board which is subsequently lowered into the plethysmograph, and which is constructed so as to diminish the interior air space as much as possible. In Fig. 2, showing a top view of the apparatus, this dog board, with

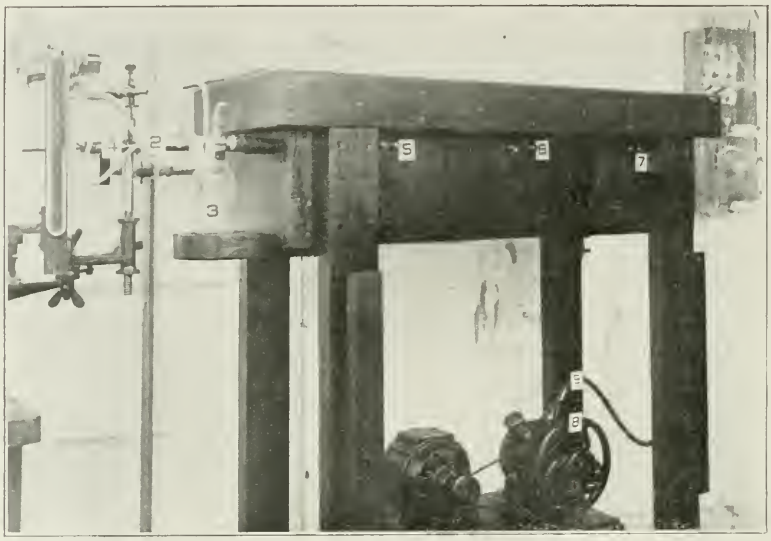

Fig. 1.—Plethysmograph showing its outside connections. *1*, Connection between mercury manometer and carotid cannula for recording blood pressure; *2*, connection with the inside of the plethysmograph for recording negative pressure changes within the plethysmograph; *3*, ether bottle connected to tracheal cannula; *4*, adjustable thumb screw valve permitting fractional pressure changes; *5* and *7*, plugs for electrical connection for stimulation of nerves; *6*, electrical connection to lamp resistance for warming interior of plethysmograph; *8*, Gaede pump; *9*, connection from exhaust pump to interior of plethysmograph.

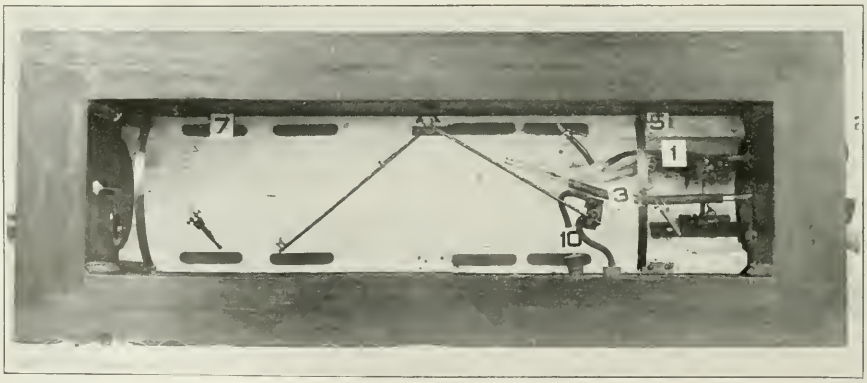

Fig. 2. Top view of plethysmograph with plate glass cover removed, showing animal holder in position and its several connections. *1*, Blood pressure tube and carotid cannula; *2*, outlet for recording negative pressure; *3*, tracheal tube and cannula; *5* and *7*, electrical connections for stimulation of nerves; *10*, return flow tubes to conduct cold fluid for freezing nerves. Support for tubes and rods for holding thermometer, as well as the headclamp can also be seen.

its handles and rods for adjustments, can be seen in position. It is also more convenient to introduce such cannulæ as are necessary for a particular experiment before placing the animal and board in position.

†Machine oil has proved more satisfactory for our purposes than has vaseline, tallow, or lighter oils.

To make connection possible between these cannulæ and recording instruments, glass tubes pass through rubber stoppers which in turn fit openings in the wooden walls. Adjustment of the stoppers to the openings is facilitated by gas pipes driven through the openings in the wood. These pipes fit tightly and are not removable. They project exteriorly and their distal openings are more readily stoppered than openings in the wood. With the exception of the exhaust (Fig. 1, 9) all the outlets are of uniform size (No. 4 rubber stopper). This uniformity has the advantage of permitting interchange of connections. The glass tubes carried by the rubber stoppers are sufficiently long to project into the

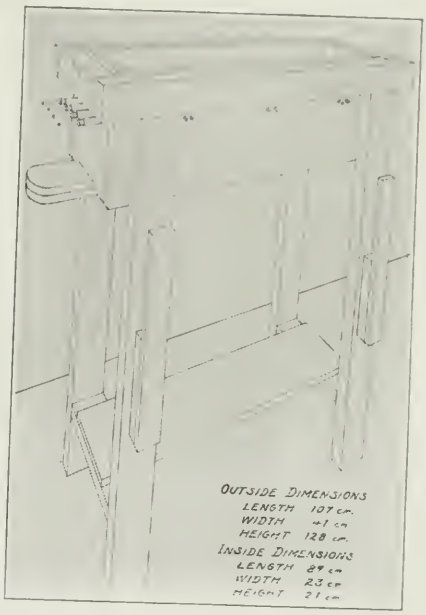

Fig. 3.—Perspective drawing of plethysmograph.

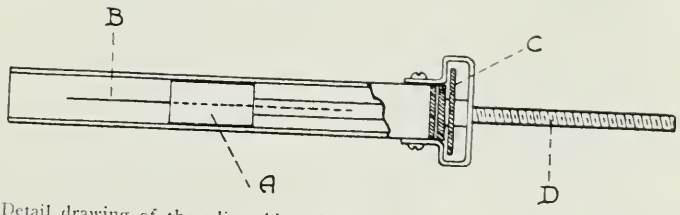

Fig. 4.—Detail drawing of the adjustable valve used to control fractional negative pressure changes within the plethysmograph. *A*, piston; *B*, slit; *C*, thumb screw; *D*, feed screw.

plethysmograph and the openings through which they pass are so placed that the tubes project interiorly above the dog board and animal.

For producing artificial distention of the lungs, the plethysmographic air is rarefied by a Gaede rotary pump. To control the plethysmographic pressure and consequent degree of lung distention, the ingress of air is varied by a regulating device (Fig. 4) of the following construction. A brass tube, 15 cm. in length and 2.25 cm. in diameter, communicates with the interior air of the plethysmograph. A slot 0.5 mm. in width is cut lengthwise through the wall of the

tube to within 2.5 cm. of its ends. This slot allows ingress of air via the cylinder to the interior of the plethysmograph. A piston accurately fitting the lumen of the cylinder prevents entrance of air from the distal end. Movement of the piston exposing a greater or shorter length of slot for the passage of air, is accomplished by a screw of small pitch passing through a threaded nut. Revolution of the nut moves the piston inward or outward. This method of controlling pressure has the advantage of obviating the influence of temperature changes within the plethysmograph, while permitting very delicate adjustment and accurate maintenance of a wide range of pressures for long periods of time.

Air is supplied to the animal's trachea through an opening in the end of the box through which, as previously described, a glass tube passes for connection with the tracheal cannula. The distal end of this tube communicates with the outside air and can be used for administration of the anesthetic. It is essential that these tubes be short in order to limit the respiratory dead space. This end is attained by an adjustable head holder on the dog board by means of which the animal's nose can be brought close to the inner wall of the plethysmograph.

In experiments necessitating artificial respiration, pulmonary ventilation is accomplished by rhythmic changes in air pressure within the plethysmograph causing alternate distention and collapse of the lungs. These pressure changes are easily effected by intermittently allowing more or less free ingress of air through one of the openings in the wall of the plethysmograph while air is being constantly withdrawn by the exhaust pump. When the opening is unobstructed it admits air freely and consequently the exhaust pump causes slight if any variation from the atmospheric pressure, but obstructions cause rarefactions of the interior air varying with the degree of occlusion. It is our belief that this method of lung inflation more closely approximates natural respiration than does intratracheal insufflation in as much as distention is accomplished, as normally, by a diminution in intrathoracic pressure.

When experiments are in progress variations of pressure within the plethysmograph are recorded by suitable apparatus communicating with the interior air. Wide variations in pressure are recorded by a mercury or a water manometer (Figs. 1 and 2) which carries a float and a recording stylus. For slight variations, a large tambour and recording lever are used. This tambour, 4 cm. in depth by 15 cm. in diameter, communicates with the interior air of the plethysmograph by means of tubing 2.5 cm. in diameter, and records the displacement of the interior air caused by natural respiration. This system is so sensitive to pressure changes and to currents of air within the plethysmograph that not infrequently heartbeats have been recorded in the respiratory tracings.

For recording blood pressure a suitable manometer, usually a mercury manometer, is connected by rubber tubing to a glass tube which fits, as previously described, an opening in the plethysmograph (Fig. 1, *1*). This system is filled with cannula fluid under pressure approximating that of an average dog and the rubber tube is clamped to prevent escape of fluid. Since this glass tube projects within the plethysmograph and would interfere with the lowering of the dog board, final adjustment is deferred until the animal is in place, when connection can be established with a cannula previously filled and inserted in the carotid ar-

tery. By similar means the pressure within the pulmonary artery may be recorded.

In the interpretation of records of blood pressure it must be borne in mind that the manometric record is affected by all factors varying the pressure within the plethysmograph and that corrections must be made by subtracting the negative pressures or adding the positive pressures. The result represents the actual blood pressure.

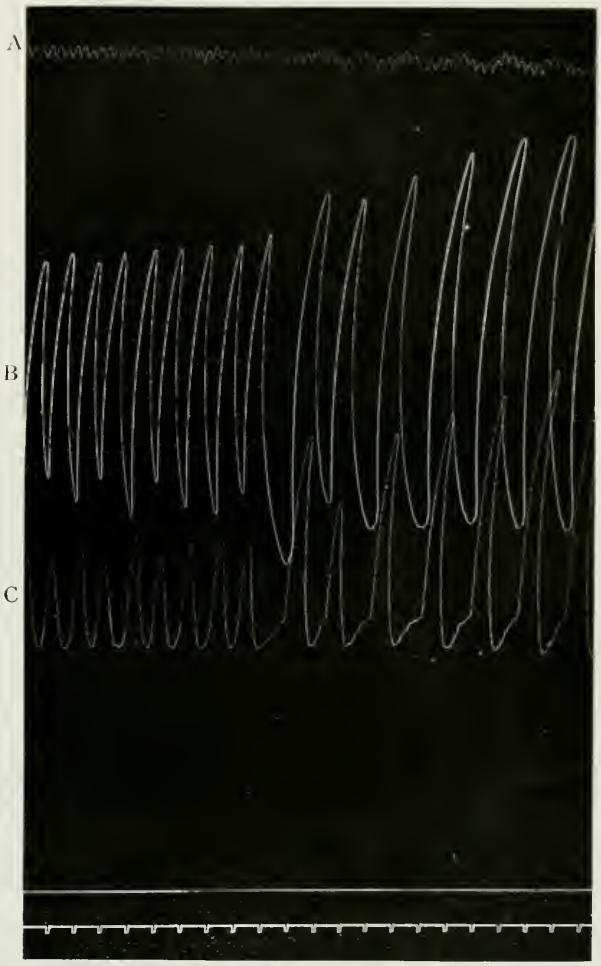

Fig. 5.—Experiment of Dec. 12, 1915. Medium-sized dog; ether anesthesia. *A*, Carotid blood pressure recorded by mercury manometer; *B*, plethysmographic curve; *C*, respiratory curve from side arm of tracheal cannula; time in seconds.

For electrical stimulation of nerves four sets of insulated binding posts on the outside of the box permit conduction of current to plugs on the interior surface. To these plugs stimulating electrodes are easily attached.

Intravenous injections are made through glass tubes fitted into rubber stoppers which in turn fit two openings in the side of the plethysmograph. These tubes are also used for establishing circulation of a freezing mixture through a suitable metallic support upon which nerves are allowed to rest.

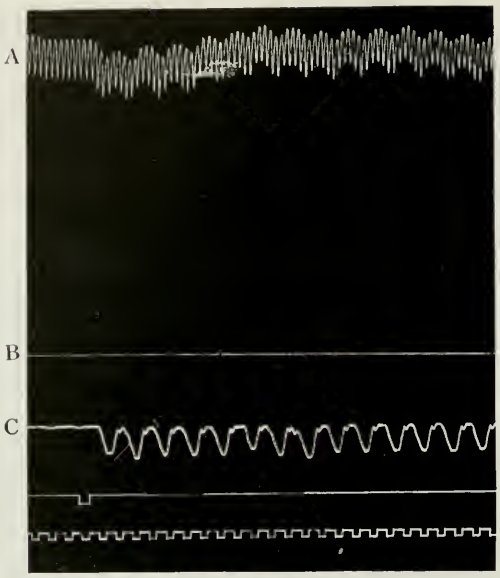

Fig. 6.—Experiment of Oct. 28, 1916. Medium-sized dog; ether anesthesia; artificial ventilation by rhythmic changes in plethysmographic pressure. *A*, Carotid blood pressure recorded by mercury manometer; *B*, abscissa for carotid blood pressure; *C*, plethysmographic pressure recorded by mercury manometer; time in seconds.

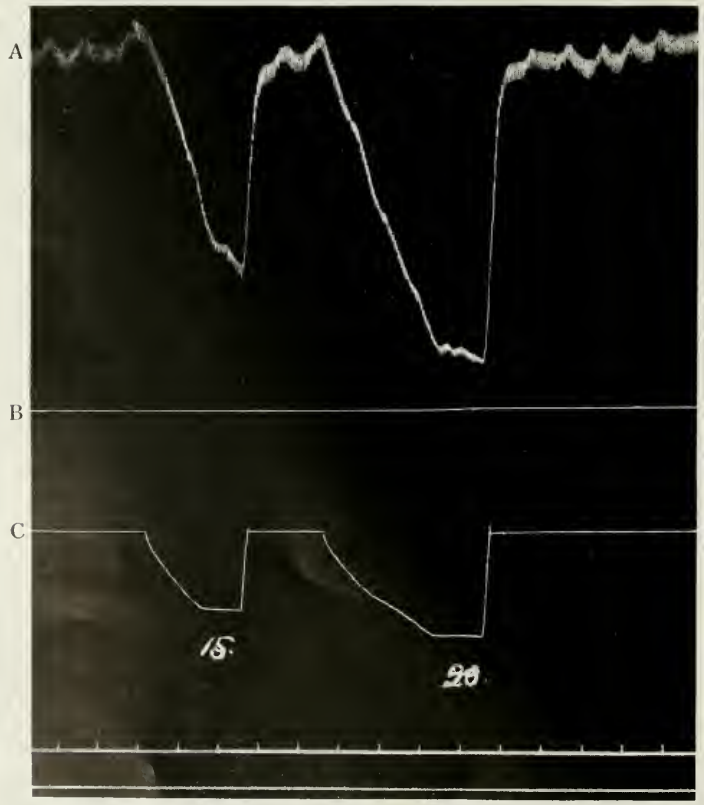

Fig. 7.—Experiment of Dec. 15, 1916. Dog 6.5 kilo; ether anesthesia. *A*, Carotid blood pressure recorded by mercury manometer; *B*, abscissa for carotid blood pressure; *C*, pressure in plethysmograph recorded by mercury manometer; time record every ten seconds.

In evidence of the adaptability and efficiency of the apparatus for recording circulatory and respiratory changes and also in maintaining constant degrees of negative pressure within the plethysmograph, five tracings are shown.

Fig. 5 shows simultaneous tracings of carotid blood pressure and two respiratory curves taken as a test of the apparatus. The period of both tambours apparently is sufficiently fast to record rapid respiration. In each of the respiratory curves the down-stroke is inspiratory and the up-stroke expiratory. The upper tracing recorded by the large tambour, is plethysmographic and the lower is from a small Marey tambour connected in the usual way with a side arm from the tracheal cannula. Both respiratory curves show changes in respiration while gradual freezing of the vagi is in progress. It will be noted that the unavoidable

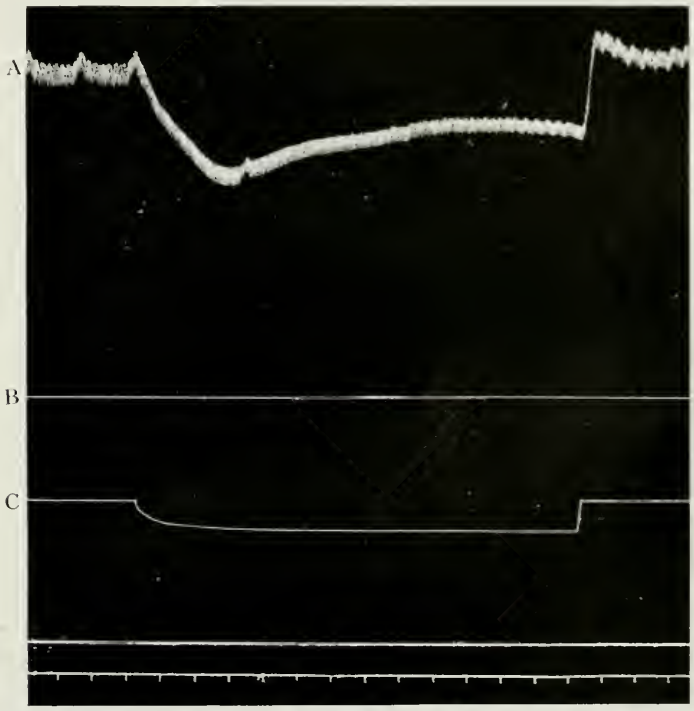

Fig. 8.—Experiment of Dec. 15, 1916. Dog 6.5 kilo; ether anesthesia. *A*, Carotid blood pressure recorded by mercury manometer; *B*, abscissa for carotid blood pressure, which is 62 mm. above the time record; *C*, pressure in plethysmograph recorded by mercury manometer; time record every ten seconds.

instrumental error in the lower tracing is absent in the upper tracing, and that the plethysmographic tracing also brings out more clearly the prolonged inspiratory phase due to abolition of function of some of the pulmonary branches of the vagi. It will further be noted that the closed system records variations in the depth of inspiration which the open system is not sufficiently accurate to register, the one recording actual volume changes and the other being affected mostly by the strength and suddenness of the expiratory blast. This closed system also has the advantage of being susceptible of calibration. The changes in blood pressure occurring as a result of freezing the vagi are not apparent in the part of the tracing shown as they occurred later.

Fig. 6 illustrates artificial pulmonary ventilation accomplished by rhythmic changes of air pressure within the plethysmograph. It will be noted that the first portion of the tracing does not exhibit in the blood pressure record the usual respiratory waves, which, however, appear with the commencement of artificial respiration which is recorded in the lower line. In this animal the chest had been previously opened.

In Fig. 7 simultaneous records of carotid and plethysmographic pressures are shown in evidence that varying degrees of negative pressure within the plethysmograph can be accurately attained and held at desired levels by the regulat-

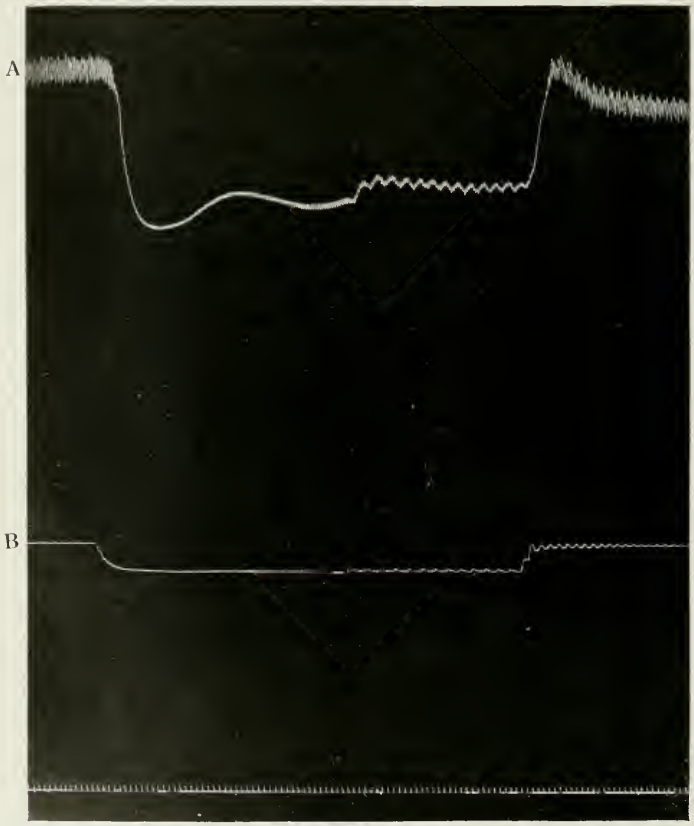

Fig. 9.—Experiment of Jan. 25, 1918. Medium-sized dog; ether anesthesia. *A*, Carotid blood pressure recorded by mercury manometer; *B*, plethysmographic pressure recorded by mercury manometer; time every second.

ing device (Fig. 4) described previously. The profound effects upon the arterial blood pressure are strikingly exemplified.

Fig. 8 shows a rapid fall in the plethysmographic pressure from zero to minus 10 millimeters of mercury and from this point during a period of 125 seconds, a further gradual fall to a minimum of minus 14 millimeters attained immediately before the release of the plethysmographic pressure. After the initial fall, the carotid pressure, in spite of this continuously falling plethysmographic pressure, shows a progressive rise of 20 millimeters of mercury within a period of 70 seconds. This higher level is maintained until the release of ple-

thysmographic pressure to the atmospheric level, when the blood pressure mounts rapidly to a level 16 millimeters of mercury above that maintained prior to the experiment. The rise in carotid pressure during the period of gradually falling plethysmographic pressure has been interpreted by us as due to systemic vasoconstriction. It was to emphasize this point that the plethysmographic pressure was gradually decreased in this experiment.

By the method of exhaustion with the Gaede pump and regulation by the device we have described, it is possible to maintain a constant degree of negative pressure in the plethysmograph for any period desired. An illustrative record of one of the shorter periods is presented in Fig. 9. In this experiment a negative pressure of 5½ millimeters was maintained for a period of 80 seconds, but the results obtained are typical of much longer periods. There is an abrupt fall of carotid pressure, then partial recovery and subsequent slight fall—constant phenomena which occur in varying degree, within moderate ranges of negative pressure. A long period of apnea occurs as a result of lung distention. In the latter half of the tracings, however, respiratory efforts show, and also an interesting rise in blood pressure coincident with the commencement of respiration.

The fall in blood pressure noted in the tracings illustrates the profound circulatory disturbance due to lung distention. With the apparatus here described these disturbances have been the subject of investigation, the results of which have furnished material which will appear in a second communication.

We are indebted to Professor W. E. Garrey for helpful suggestions and criticism.

SUMMARY

A plethysmograph is described which is large enough to hold a medium sized dog. It permits of varying the distention of the lungs by exhausting the interior air and the degree of fall in pressure is controlled by a device described in the text. Pulmonary and carotid pressures and other circulatory conditions as well as the pressure within the plethysmograph may be recorded manometrically. The vagi and other nerves may be frozen or stimulated, the anesthetic varied, and artificial respiration resorted to without interrupting the experiment or opening the plethysmograph. Experiments showing some of the applications and the methods and their results are briefly described.

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LABORATORY METHODS

SIMPLIFIED GAS ANALYSIS

NO. III. THE DISSOCIATION CURVE FOR OXYGEN AND THE CO_2-COMBINING POWER OF BLOOD

By J. J. R. Macleod, M.B., and R. S. Lang, B.A., Toronto, Canada

FOR accurate determination of the relative amounts of reduced and oxyhemoglobin in blood exposed to atmospheres containing varying partial pressures of oxygen no method surpasses that of Barcroft and his coworkers.[1]

The principle of this method is to expose a small quantity of blood in a thin film on the walls of a relatively large cylindrical vessel (tonometer) containing a mixture of nitrogen and oxygen gases until equilibrium has become established between the partial pressure of the oxygen in the atmosphere and the absorption of oxygen by the blood. Some of the blood is then transferred to a bottle connected with a differential manometer and shaken with dilute ammonia water, by which it becomes laked and takes up its maximal load of oxygen, thereby causing shrinkage in the volume of air, the degree of which is indicated by the manometer. The oxygen-saturated blood is then shaken with ferricyanide of potassium which dislodges the oxygen and causes the pressure in the bottle to rise. From the displacement of the fluid in the manometer in the two observations, the percentage of saturation of the blood with oxygen is readily calculated.

For use by a class of students the method is not practical because of the difficulty of providing suitable mixtures of oxygen and nitrogen with which to fill the tonometer and because of the expense of the differential manometer. The first of these difficulties is overcome by exposing the blood to a partial vacuum instead of a mixture of gases, a principle which has also been applied by W. G. Macallum, who uses a modified Van Slyke pipette both as tonometer and analysis apparatus.[2] The advantage of a partial vacuum over a mixture of oxygen and nitrogen is that the partial pressure of oxygen is readily calculated from the degree to which the tonometer is evacuated as measured by a barometer. In the present method the blood after exposure to the partial vacuum is transferred to a simple form of differential blood gas manometer in which there are no glass stopcocks, pressure adjustment being made by the use of the pressure adjuster described elsewhere.[3] Even with these simplifications, the technic is by no means easy, but the great importance of having the student clearly understand the principles of the method used for securing the data necessary to plot the dissociation curve amply repays the time he devotes to the experiment. Indeed without actually doing this experiment, it is the opinion of the writers that the average student rarely acquires any clear conception of the respiratory function of the blood. After he has conscientiously performed the experiment, on the other hand, the whole problem becomes clearer, even although results that are

absolutely correct may not have been secured. A laboratory session of at least three continuous hours is essential, and the students can most profitably work in groups of three each.

DESCRIPTION OF THE APPARATUS

The Tonometer.—This consists of a wide glass tube (the tonometer *T*, Fig. 1) of fairly stout glass, tapering down to narrow tubes at both ends. The capacity should be at least 200 c.c.* The narrow tubes are connected with thick-walled (pressure) rubber tubing which should be wired on to the glass tubes. The rubber tubes are closed by screw clips (1 and 2). File marks are made at

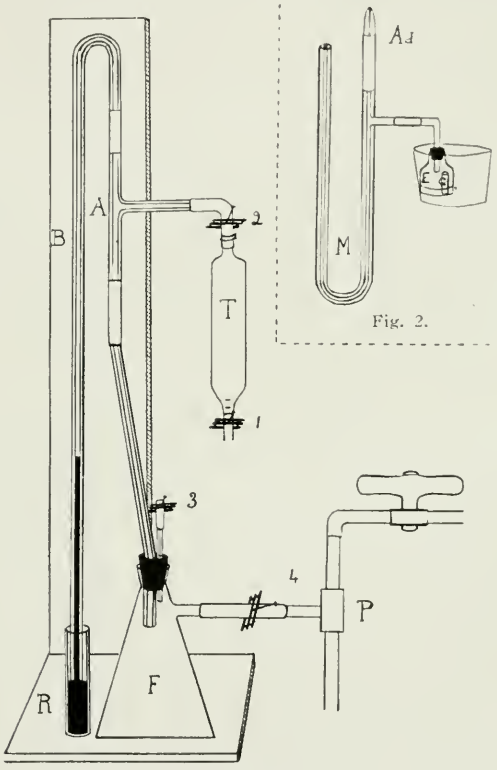

Fig. 1.

one of the tapering ends of the tonometer, the distances between them corresponding approximately to one cubic centimeter.

The Barometer.—This consists of a vertical, thick-walled glass tube about 1.25 meters long and of about 3 mm. bore bent on itself near one end, and with the other end dipping into mercury contained in a wider flat-bottomed (specimen) tube (the mercury reservoir) closed by a perforated cork. The barometer tube and reservoir are firmly mounted on a stand furnished with a millimeter scale which is attached to the stand in such a way that it can be adjusted to bring its zero to the surface of mercury in the reservoir, as this varies at different pressures. The free end of the barometer tube is connected by rubber pres-

*It would be preferable to use a tonometer two times as large since this would diminish errors due to the addition of the gas given off from the blood.

sure tubing to a glass T-piece (*A*), one limb of which is similarly connected to a stout-walled (filtration) flask (*F*) joined to a good water pump (*P*). A capillary tube closed by a piece of rubber tubing and a screw clip (*3*) also passes through the stopper of the flask.

The Differential Manometer and Gas Bottle.—This apparatus requires a piece of narrow bored glass tubing (bore 1 mm.) bent into a U-shape with one limb about 200 mm. long and the other about 150 mm. (*M* in illustration). To the shorter limb is connected a T-piece (of narrow bore tubing) which should be fused to it, although rubber pressure tubing is quite satisfactory. One limb of the T-piece is connected with red rubber tubing of moderately thick wall, closed by a pressure adjuster (Ad) as described elsewhere.* By pinching the rubber tubing lying over the lateral hole of the adjuster, the manometer is brought into communication with the outside so that the air in the bottle and manometer are brought to atmospheric pressure. The other tube of the T-piece is connected by pressure rubber tubing with a glass tube which passes through a rubber stopper that accurately fits a small wide-mouthed bottle *E* of about 15 c.c. capacity. Finally a small flat-bottomed test tube 15 mm. high and 6-7 mm. diameter is required, *I*. Instead of attaching the T-piece to the short limb of the manometer, it may be inserted in the rubber stopper, one limb being connected with the manometer—which in this case simply consists of a U-tube—and the other with the pressure adjuster. The fluid used in the manometer is clove oil.

TECHNIC OF ANALYSIS

The tonometer is rinsed out with physiologic saline and is connected with the side tube of the barometer T-piece *A*. The pump *P* is turned on with screw clips *1* and *3* closed, but screw clip *2* open and the pressure lowered until the mercury stands at a constant level in the barometer. Screw clip *4* is closed and the mercury observed to see whether there is any leak. Provided there is none, clip *3* is cautiously opened and the mercury allowed to fall almost to the level in the reservoir (*R*); clip *2* is tightened, the tonometer, *T*, removed, and the pump turned off. Defibrinated or oxalate blood (whipped ox blood is most suitable for large classes, but in any case blood from an etherized animal must not be used) is now sucked into the tonometer, by placing some of the blood in a small evaporating dish and cautiously loosening clip *1* with the rubber tube dipping into the blood; *3* to *4* c.c. of blood should be allowed to enter the tonometer. This is then reattached to the T-piece *A* of the barometer and with clips *2* and *4* open (but *1* and *3* closed) the pump is turned on and the mercury allowed to rise as far as it will go, when clip *4* is closed and the pump turned off. Clip *3* is now cautiously opened until there is a partial pressure of about 20 mm. Hg oxygen in the tonometer.†

*This Journal, iv, 69.

†This is computed as follows: After suitable adjustment the standard barometer in the room is read and from the reading is subtracted the tension of aqueous vapor at the temperature of the room (for table see page 420 of this Journal, Vol. III). The difference gives the pressure in mm. Hg of an atmosphere of dry air. Since air contains 20.96 per cent oxygen, the partial pressure of this gas in the tonometer must be equal to $\frac{20.96}{100}$ of the difference between the height to which the mercury is raised in *B* and the corrected barometer reading. Thus, suppose the room barometer is 753.4 mm. and aq. tension 17.4 mm. the corrected barometer reading is 753.4-17—4 = 736 mm. Then $\frac{20.96}{100} \times 736 = 154.2$ mm. O_2.

$$20 \text{ mm. } O_2 = \frac{20 \cdot 736}{154.2} = 95.45 \text{ mm.}$$

That is the mercury in the barometer must be raised to 736 − 95.45 640.55 mm.—above the level in the reservoir (*R*).

When the mercury has reached this level, or one near it, clip *3* is closed and the height at which the mercury stands very accurately noted. Clip *2* is then closed, after which the mercury is allowed to fall to zero by opening *3*. The tonometer is now removed and rotated so that the blood becomes spread out as a thin film on the walls, after which it is placed in a water-bath kept at about 40° C. in which it is constantly rotated for about 15 minutes.

On removal from the bath the pressure in the tonometer must again be measured. For this purpose the tonometer is reattached to *A* and the pump is turned on (with *3* closed) until the mercury has risen to the level at which it previously stood. Clip *1* is closed and *2* opened. If there has been no leak, and time has been allowed for the tonometer to cool down, there will be practically no difference between the two readings. If a difference of more than 5 mm. is observed it must be noted and the pressure prevailing in the tonometer taken as the average between the two readings.

Meanwhile 3 c.c. of freshly prepared weak ammonia water containing a trace of saponin (0.5 c.c. aq. ammonia in 500 c.c. water) has been placed in the blood gas bottle *B*. A pointed glass tube about 30 mm. long is now attached to the rubber tubing of the tonometer and this is removed from the barometer and held in vertical position above the bottle. The screw clip *2* is opened so that the air enters the tonometer, the clip *1*, is then cautiously opened to let a drop or two of blood flow out from the tip of the glass tube,* and after closing it again the end of the tube is wiped free of blood and placed in the bottle so that it dips under the ammonia solution. Clip *1* is now cautiously opened and about 1 c.c. of blood allowed to flow under the ammonia water. If this is done carefully the blood does not mix with the ammonia water which floats on the top of it as a layer and so prevents any diffusion of oxygen between the blood and the air. The bottle is firmly closed by its stopper, the pressure adjuster being meanwhile held open so that the level of the clove oil in the manometer is not disturbed. The bottle must now be submerged in a water-bath containing water at about room temperature, in which it is left until, with the adjuster closed, no further contraction of volume, due to cooling, is observed to occur.

The bottle is now removed from the bath and vigorously shaken so that the blood becomes laked and absorbs O_2 from the atmosphere of the bottle. After replacing the bottle in the bath and allowing time for cooling the difference between the levels of clove oil in the two limbs of the manometer is noted. With the adjuster open to the outside the stopper is removed from the bottle and about 0.25 c.c. of a freshly prepared saturated solution of potassium ferricyanide is placed in the small flat-bottomed test tube which is then lowered by means of a forceps into the fluid in the bottle, without allowing any of the ferricyanide to mix with the laked blood. After reinserting the stopper and cooling, the bottle is again removed from the bath and shaken so that the ferricyanide by mixing with the laked blood drives off the loosely combined oxygen and raises the pressure, which is measured by the manometer.

The relative amounts of reduced and oxy-hemoglobin present in the blood are proportional to the first and second readings of the manometer; when all is reduced hemoglobin the diminished pressure (shrinkage) recorded in the first

*Enough blood should be run out to bring the meniscus of blood in the tonometer to the upper file mark.

shaking of the bottle is practically the same as the increased pressure recorded in the second. They will not be exactly the same, since the volumes of bottle and tubing in the two cases are not the same, but the error thus incurred is inconsequential for most purposes (cf. Boyle's law).

The calculation of the percentage saturation of hemoglobin with oxygen is made by subtracting the first reading from the second, dividing by the second reading and multiplying by 100. Suppose in the observation made at 20 mm. partial pressure of O_2 the first reading is 24 mm. and the second, 108, then

$$\frac{108-24}{108} \times 100 = 77.7\% \text{ HbO and } 22.3\% \text{ Hb.}$$

The result must now be plotted on coordinate paper with the percentages of HbO along the ordinates and the partial pressures of oxygen on the abscissæ.

The observation is repeated at different pressures and by joining the points, the dissociation curve for blood is obtained. Care must be taken to see that the bottle is sufficiently shaken so that the partly reduced blood absorbs all the oxygen and gives it up again with ferricyanide. It is particularly in the latter operation that care must be taken.

The influence of carbon dioxide in lowering the dissociation curve can be readily shown by the method. The procedure is as follows: After the pressure has been reduced to the desired degree in the tonometer, the latter is placed in a horizontal position so that the blood lies along the walls, free of the ends. A CO_2 generating apparatus (Kipp's) or a bottle containing this gas is then connected by suitable tubing with the free end of the tonometer, care being taken before making the connection, to fill the tubing with CO_2. To accomplish this a slow stream of the gas is maintained and the air in the tubing beyond the screw clip (*1*) is squeezed out before connecting with the CO_2 generator. The most suitable partial pressure of CO_2 to work with is 40 mm. which is secured by cautiously opening screw clip *1* until with clip *2* open, but *3* and *4* closed, the mercury descends through 40 mm. in the barometer. Clips *1* and *2* are then tightly screwed down, and the tonometer removed, the further procedure being exactly as described above.

The effect of the 40 mm. of CO_2 will be found in the above example where a partial pressure of 20 mm. O_2 was used to reduce the percentage of HbO from 77 to about 35.

THE CO_2-COMBINING POWER OF THE ALKALINE RESERVE OF THE BLOOD

After completing the estimations necessary for finding the percentage of oxyhemoglobin, in the experiments in which CO_2 is present in the tonometer, it is of interest to determine the amount of this gas with which the blood has combined. This will represent its ability to act as a buffer towards foreign acids. To perform the estimation it is necessary, however, to measure accurately the amount of blood which is removed from the tonometer to the blood gas bottle. This can readily be done by attaching a 1 c.c. pipette to the tubing of the tonometer (beyond clip *1*), a few drops of blood being allowed to escape from the pipette before delivering under the ammonia solution in the bottle, and precautions being taken not to take any of the upper layers of blood that had been exposed to full

atmospheric pressure when the tonometer was opened. This is done by removing the pipette from the tonometer before all the blood has run out.

To dislodge the CO_2 from the blood, the stopper is removed with the usual precautions and about 0.25 c.c. of a saturated solution of tartaric acid placed in the small test tube. After closing and allowing for temperature changes, the acid is shaken with the mixture of blood and ferricyanide, and the CO_2 thereby evolved measured by multiplying the displacement of the fluid in the manometer by a figure (the constant of the apparatus) obtained by a preliminary experiment in which a known amount of a standard carbonate solution is similarly treated.

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AN APPARATUS FOR VOLUMETRIC SODIUM HYDRATE*

By Ralph R. Mellon, M.Sc., M.D., Dr. P.H., Rochester, N. Y.

THE variability of volumetric NaOH solutions as a result of the ease with which chemical combination is effected with CO_2 of the air is too common an experience to require comment. Accordingly I have devised an apparatus with which it is possible to keep such a solution indefinitely. The principle, exceedingly simple, makes use of the difficulty just mentioned, by freeing all air that comes in contact with the solution by previous contact with a concentrated solution of the alkali. Additional provision may be made for drying the same air with $CaCl_2$.

Given a bottle with outlet at the base, a burette stand and properly constructed burettes, anyone with a rudimentary knowledge of glass-blowing can construct the apparatus as above represented in a short time. The larger bottle (*A*) contains the volumetric solution, and the smaller one (*B*), the concentrated solution (10 per cent) of NaOH. *B* has a two-holed rubber stopper, one hole being occupied by a U-tube (c), the inner end of which is immersed in the solution, while the outer end permits the entrance of air to be freed from CO_2 in its passage through the 10 per cent NaOH. The other hole of the bottle is occupied by a straight piece of glass tubing, the inner end of which is not in contact with the solution, while the outer end leads to a filled $CaCl_2$ tube, by way of a flexible rubber tube (*d*). A gas-washing bottle of any convenient size could, of course, be used.†

The large bottle (*A*) has a one-holed rubber stopper which admits a glass (*T*), the lateral branch of which anastomoses with the $CaCl_2$ tube; the other

*From the Department of Laboratories, Hahnemann Hospital, Rochester, N. Y.

†A very helpful criticism of this apparatus has been made by a friend who has used a similar type. His experience has occasionally been that the expansion of the air above the solution forces the concentrated NaOH out of the U-tube (*C*). I have never had this experience, although, as he says, my apparatus may not be completely air-tight; yet the contained solution has never shown visible precipitate in the course of a year. In his own apparatus he is using a simple device remedying this defect, but I do not feel at liberty to appropriate it.

branch, after being bent at right angles, leads to the discharging burette (*E*). Of the two openings at the bottom of the latter, one is an outlet provided with a glass stopcock (*s*), the other an inlet similarly equipped, which receives the solution from the outlet (*o*) at the base of bottle *A*. These openings are connected by a piece of rubber tubing wired on at either end, and provided with a clamp as an additional precaution. The upper end of burette *E* admits a one-holed rubber stopper, which in turn gives passage to a T-shaped glass tube (*F*). Both branches of the *T* outside the burette are bent at right angles, one connecting with the free arm of the glass *T* in Bottle *A* by rubber tubing, the other attached to a piece of rubber tubing kept tightly closed with a Hoffman clamp. Burette *E* is held by clamp of stand *H*, in which I find it convenient to have an additional empty burette.

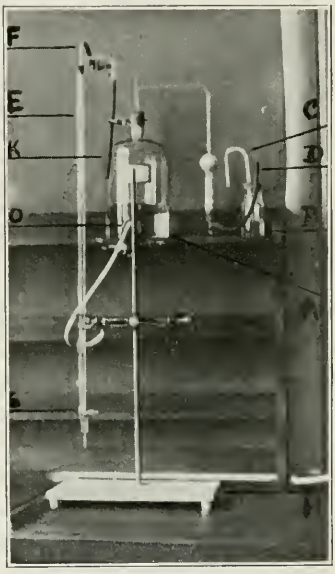

Fig. 1.

The apparatus is wholly portable. The flexible rubber tube (*d*) in bottle *B* makes it possible to hold both bottles in the right hand, while the standard of the burette stand may be grasped with the left hand. This is of advantage, especially when it is necessary to replace the CO_2 containing air above the solution and in the connecting tubes with CO_2 free air. This is only necessary when the NaOH solution is first put in bottle *A*. At this time the apparatus can be carried to the aspirator, to which it is connected by tube (*k*). The aspiration is continued until the air from *k* reacts negatively with $BaCl_2$. This test is made by attaching temporarily a rubber tube to U-tube *C*, immersing tube *k* in $BaCl_2$ solution, into which the contained air is forced by blowing into U-tube (*c*). The glass connecting tubes, including the one containing the $CaCl_2$, we readily made with a blast lamp.

TECHNIC FOR THE WASSERMANN REACTION*

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New York City

THE following technic is employed at the City Hospital Pathological Laboratories in performing the Wassermann reactions. It is, in its essential details, the Wassermann-Citron technic, with certain modifications in accordance with the more recent research advances in this field.

VOLUME

The total volume of the reactions is 2.5 c.c., being one-half the amount of the original volume used by Wassermann and his coworkers. Each ingredient is diluted, in accordance with preliminary titrations, so that for the test .5 c.c. of each ingredient is added. The figures given below apply to the original Wassermann amounts, and for their application to our work are divided by two.

PREPARATION OF SERA

Blood sera are sent to the laboratory on the afternoon of the day previous to that on which tests are performed. They are allowed to coagulate and stand at room temperature from one-half to two hours. The clots are then carefully separated from the sides of the tubes with a fine sterile wire and the tubes placed in the ice chest overnight. On the following morning the sera are poured off or pipetted from the clots, centrifugalization being resorted to only in cases where the sera are not clear and free from cells.

All sera are inactivated in a water-bath at 55° C. for one-half hour.

HEMOLYTIC SYSTEM

The hemolytic system consists of sheep cells and antisheep hemolytic amboceptor derived from rabbits.

CORPUSCLES

Corpuscles are obtained fresh from an abattoir on the day previous to that on which the tests are performed. The whole blood is collected in a sterile glass bottle, tightly stoppered and containing glass beads. It is defibrinated by gentle shaking for fifteen to thirty minutes. After defibrination it is filtered through twelve thicknesses of sterile gauze to remove any small clots of fibrin including, in their meshes, cells. The filtrate is placed in 15 c.c. centrifuge tubes and centrifuged four times at high speed. The first centrifugalization is for 25-30 minutes. The pure serum is then pipetted off and the cells well mixed with .9 per cent sterile saline. The second, third and fourth centrifugalizations are for 25, 15 and 15 minutes respectively, the saline being pipetted off and fresh saline added each time. Samples of blood showing any hemoglobin tinge in the super-

*This article is published as a supplement to "The Value of the Wassermann Reaction. A Reply," published in Jour. Am. Med. Assn., June, 1, 1918, p. 1589.

From the Pathological Laboratories, City Hospital, New York City

natant saline after the third or fourth centrifugalization are discarded. The washed corpuscles are placed in the ice chest overnight, and on the following morning a 5 per cent suspension of the packed corpuscles is made up for titrations and tests.

COMPLEMENT

Guinea pig complement is obtained by bleeding to death from the carotid artery from three to five, preferably the latter, animals. Average-sized animals, 250 to 500 grams, are selected when this is possible, and they are not fed for at least twelve hours before the bleeding. Unnecessary excitement of the animals is avoided. The complement is obtained in the late afternoon preceding the day of the tests. It is allowed to coagulate at room temperature; the clot is separated with a small sterile wire, and the containers (15 c.c. centrifuge tubes) are placed in the ice chest overnight. On the following morning the serum is pipetted off and centrifuged once at high speed, until all cells are thrown down. It is then pipetted to another sterile container and placed in the ice chest until used. This usually yields a clear, slightly yellowish serum. A slight hemoglobin tinge is of no particular importance.

AMBOCEPTOR

The antisheep hemolytic amboceptor is placed in small, sealed sterile ampules after inactivation at 56° C. for one-half hour. Each ampule contains approximately 5 c.c., and they are kept in the ice chest near the ice.

PRELIMINARY TITRATION OF HEMOLYTIC SYSTEM

Amboceptor.—Each batch of amboceptor is tested for its hemolytic titer with 1 c.c. of 1:10 dilution of complement from 3-5 guinea pigs and 1 c.c. of 5 per cent sheep cell suspension. This titration is repeated on four or five occasions with different batches of complement and the average minimal amount

TABLE I

TITRATION OF ANTISHEEP HEMOLYTIC AMBOCEPTOR—RABBIT IMMUNE SERUM

TUBE NO.	1	2	3	4	5	6	7	8	9	10	11
Amboceptor 1:500	0.5	0.45	0.4	0.35	0.3	0.25	0.2	0.15	2.0	0.0	0.0
Saline .9%	0.5	.55	0.6	0.65	0.7	0.75	0.8	0.85	0.0	0.0	0.0
Complement 1:10	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	0.0	1.0	0.0
Saline .9%	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	3.0	4.0
Cells, 5% emulsion	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Incubation, water-bath, 1 hr., 37.5° C.	...	...	...	...	...	...	...	...	...	...	...
Resulting hemolysis	C	C	C	C?	marked	med.	sl.	0	0	0	0

which causes complete hemolysis (perfectely clear red solution with no turbidity or sedimented cells) at the end of one hour in the water-bath at 37.5° C. is recorded as the unit titer for that amboceptor. Before each group of reactions the titration of the amboceptor is repeated with the pooled complement of that day as a check. Table I illustrates the order used for the addition of the ingredients

for the titration of the amboceptor before every series of tests. For the reaction two units are always employed.

Complement.—Each batch of pooled complement is titrated against an excess (2 units) of amboceptor, the unit of amboceptor having been previously determined, as described above. One unit of complement is that amount which produces complete hemolysis (perfectly clear red solution with no turbidity or sedimented cells) at the end of one hour in the water-bath at 37.5° C. Table II illustrates the order used for the addition of the ingredients in the complement titration. For the reaction two units are employed.

One actual unit of amboceptor on the basis of the above titration lies between .35 and .4 c.c. of the dilution of amboceptor employed (1:500). For practical purposes .35 might safely be used, but .4 is taken to be the full unit, and the amboceptor is diluted 1-625 and 1 c.c. of that dilution added for the test, this being the equivalent of .8 c.c. of 1-500 dilution or two full units. As stated, for practical purposes, .35 c.c. of the 1:500 dilution is one unit and .7 c.c. two units, so that the 1 c.c. of the 1:625 dilution, employed in the reaction, represents practically three units.

The method given below for the readings of the degree of hemolysis will illustrate that complete hemolysis is that degree which results in a perfectly clear, red solution with no turbidity or sedimented cells at the end of the prescribed period of one hour. Slight differences occur, if identical titrations are done in duplicate at the same time, by the same person and with the same reagents. In other words, a certain latitude must be allowed for the unavoidable error in the standardization of pipettes and for the human error that can not be compensated for. The same remarks apply to the complement titration shown in Table II.

All amboceptor dilutions are made from one original dilution of 1:1000, a sufficient amount of this being made for the day's work.

All complement dilutions for titrations are made from one original dilution of the pooled complement of 1:5.

So far as feasible, the same pipette is used for diluting the amboceptor and for adding it to the several tubes. The same precaution is also taken in adding the complement to the tubes of the complement titration.

Saline from one flask containing a sufficient amount for one day's work is employed for all titrations and tests. So far as feasible, but one pipette is used for saline.

TABLE II

TITRATION OF COMPLEMENT

TUBE NO.	1	2	3	4	5	6	7	8	9	10	11
Complement 1-10	0.8	0.6	0.5	0.45	0.4	0.35	0.3	0.25	1.0	2.0	3.0
Saline .9%	0.2	0.4	0.5	0.55	0.6	0.65	0.7	0.75	0.0	0.0	0.0
Amboceptor 1-625	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	0.0	0.0	0.0
Saline .9%	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	3.0	2.0	1.0
Cells 5% Emulsion	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Incubation water-bath 1 hr. at 37.5° C.	...	...	...	...	...	...	...	...	...	...	...
Resulting hemolysis	C	C	C	C	C?	marked	med.	sl.	0	0	med.

With two full units of amboceptor as determined by the titration in Table I one full unit of complement equals .45 c.c. of a 1:10 dilution. For the reaction .9 c.c. of a 1:10 dilution is employed. The actual unit of complement as determined from the above titration lies between .4 and .45 c.c. We do not consider that a greater number of dilutions are feasible for practical work. From a practical standpoint .4 c.c. of the 1:10 dilution represents one unit and .9 c.c. approximately 2¼ units.

Ingredients are added in the order shown in the tables above. After the addition of each ingredient, the mixture is thoroughly shaken. For the test each ingredient is made up in such dilution that 1 c.c. of each is added, with the exception of the complement. During the incubation of the titrations and tests the tubes are shaken at fifteen-minute intervals.

Controls are made for the following:

Isohemolytic	activity	of	amboceptor in excess (5 units)	Tube	9,	Table	I
"	"	"	saline	"	11,	"	I
"	"	"	complement	"	10,	"	I
"	"	"	"	"	9,	"	II
"	"	"	"	"	10,	"	II
"	"	"	"	"	11,	"	II

Complements which show any more than a slight isohemolytic activity in an amount slightly in excess (.2 c.c. of 1:10 dilution) of the amount that represents two units or that are of very weak hemolytic activity (.8 c.c. of 1:10 dilutions) with the excess of amboceptor are discarded.

The following method is used for readings of hemolysis:

Clear, red, no turbidity or sedimented cells—complete	.... or 4-plus	hemolysis (100%)
Slight turbidity, but no cells—complete?	.... or 4-plus?	" (100%?)
Turbidity with few (25%) cells—marked	.... or 3-plus	" (75%)
50% sedimented cells—moderate	.... or 2-plus	" (50%)
75% " " —slight	.... or 1-plus	" (25%)
100% " " —none	.... or 0	"

ANTIGENS

Three antigens are employed routinely: (1) a cholesterin reinforced antigen, either human or guinea pig heart; (2) an alcoholic extract of beef, guinea pig or human heart; (3) an alcoholic extract or Noguchi acetone-insoluble lipoidal antigen.

As is well known, antigens made at different times and by different methods or with different tissues vary greatly in their fixing property. It is usually true in our work that we have antigens with varying degrees of fixing power. The first antigen is always the strongest and the second and third respectively, weaker. In this manner we can estimate the relative strength of positive reactions. New antigens are never used for routine work until their comparative strengths have been tested out with old antigens of known strength, with from two to five hundred different blood sera.

METHOD OF ANTIGEN PREPARATION

Guinea Pig Heart.—1. Hearts are removed and dissected free from fat and other extraneous tissue. They are washed free from blood in .9 per cent saline.

2. Washed hearts are placed in absolute alcohol and kept at room temperature, until approximately 100 have been collected.

3. Alcohol is poured off; hearts are finely minced; dried and weighed.

4. Absolute alcohol is added in the proportion of ten volumes to one volume of heart tissue, using the alcohol in which the hearts were originally collected.

5. The alcoholic extract is placed in the thermostat at 37.5° C. for 14-21 days, being shaken at least once daily.

6. The alcoholic solution is filtrated off and the antigen titrated for its antigenic, anticomplementary and hemolytic doses.

Alcoholic extracts of human and beef hearts are prepared in the same manner as those of guinea pig hearts, with the omission of step two and the first part of step three. Acetone-insoluble, ether-soluble lipoidal antigens are prepared in accordance with the method outlined by Noguchi.

Alcoholic extracts are reenforced by the addition of .4 per cent Kahlbaum's cholesterin. Small quantities of alcoholic extracts are reenforced with cholesterin at frequent intervals, so that they are used up within from three to four weeks.

ANTIGEN TITRATIONS

All antigens are tested for the minimal antigenic, anticomplementary, and hemolytic doses. It is not considered necessary here to detail the protocols for these titrations. With cholesterinized antigens the dose employed in the test is from five to twenty times the minimal antigen dose, or that dose producing complete inhibition with several (3-5) pooled positive sera. The precaution is taken to select sera that are not anticomplementary in double the amount used for the test (.4 c.c.), and that have no natural antisheep amboceptor. No more than one-fifth the anticomplementary or hemolytic dose of cholesterinized antigens is ever used. The latter factor seldom renders any of our antigen useless, but the anticomplementary feature is of the utmost importance.

An average titration of our cholesterin-reenforced guinea pig heart and human heart antigens is represented as follows:

Minimal antigenic dose (with pooled positive sera)	0.005 c.c. of undiluted antigen
Anticomplementary dose	0.35 " " " "
Hemolytic dose	0.45 " " " "

For the reaction 1 c.c. of a 1:20 dilution (the equivalent of .05 c.c. of the undiluted antigen) is employed.

In the case of simple alcoholic extracts and Noguchi antigens the dose in the test represents two or three times the minimal antigenic dose, and never more than one-half the minimal anticomplementary dose. In practice our antigens have such wide differences between the antigenic and anticomplementary doses that the limits are much greater than this.

The order for the addition of ingredients in the titrations of antigen is as follows:

For antigenic dose:

Antigen, plus saline,	1 c.c.
Pooled positive serum, plus saline,	1 c.c.
Complement, plus saline, (2 units)	1 c.c.
Incubation water-bath 1 hr. at 37.5° C.	
Cell suspension 5 per cent Amboceptor (2 units) Sensitized for ½ hr. in water-bath	2 c.c.

For anticomplementary dose the same with the omission of positive serum, the total volume being made to 5 c.c. with saline.

For hemolytic dose the same with the omission of positive serum and amboceptor, the total volume being made to 5 c.c. with saline.

REACTION

1. The original Citron method of using two tubes for the reaction proper, the second tube containing one-half the dose of antigen and serum used in the first tube has been followed for the first two antigens. With the third antigen only one tube with the full dose of antigen and serum is used. Each serum is controlled for its anticomplementary property with double the amount used in the test proper.

2. Owing to the necessity of conserving reagents, the Citron method has been modified to the extent of omitting the second tube in all recent work.

Metal racks with two rows are used, and the tubes are set up as follows:

Method I

1. Citron method for first two antigens; single tube for third.

	Front row			Back row		
Tube	1	2	3	1	2	3
Tube No.						
Antigen	1.0 c.c.	1.0	1.0	0.5	0.5	0.0
Saline	0.0	0.0	0.0	0.5	0.5	1.0
Serum	0.2	0.2	0.2	0.1	0.1	0.4
Saline	0.8	0.8	0.8	0.9	0.9	0.6
Complement 1:10	0.9	0.9	0.9	0.9	0.9	0.9
Saline	0.1	0.1	0.1	0.1	0.1	0.1

Incubation for 1 hour in water-bath at 37.5° C.

Cell suspension 5% Amboceptor diluted so that 1 c.c. equals 2 full units. } Equal parts of cell suspension and amboceptor sensitized in thermostat for one-half hour 2 c.c. to each tube.

Incubation until controls completely hemolyze; usually 20 to 30 minutes.
First reading immediately.
Second reading after standing overnight at room or ice box temperature.

2. Method identical with that detailed above, with the exception of the omission of tubes 1 and 2 in back row, two antigens being placed in the front row; viz., a cholesterin and alcoholic extract; one antigen placed in first tube of back row; viz., another alcoholic extract or a Noguchi antigen; serum control placed in second tube of back row.

METHODS OF READING

With the Method I the Citron method of degree reading is used for the first two antigens (Antigen 1 cholesterinized—Antigen 2 strongest noncholesterinized antigen, either sample alcoholic extract or Noguchi), and merely a positive or negative reading on third antigen.

With Method II the Citron method has been modified so that the weaker antigen used in the second tube is considered as though it were the same as the half amount of antigen and serum tube (back row 1 and 2) of the original method.

INTERPRETATION OF WASSERMANN READINGS

The readings of antigen No. 3 (See Method I) are omitted because they are always weaker than those of the second antigen. Many of the combinations shown above occur seldom, or never, the second antigen in practically every case giving complete hemolysis in the reaction before there is any hemolysis shown with the cholesterinized antigen (No. 1).

Method I

ANTIGEN NO. 1 CHOLESTERINIZED	ANTIGEN NO. 2 NEXT WEAKER ANTIGEN	ANTIGEN NO. 3 SECOND WEAKER ANTIGEN	INTERPRETATION
	4-plus		Very strongly positive
4-plus	3-plus		" " "
4-plus	2-plus		" " "
4-plus	1-plus		Strongly positive
4-plus	Doubtful		" "
3-plus	3-plus		" "
3-plus	2-plus		" "
3-plus	1-plus		" "
3-plus	Doubtful		" "
4-plus	Negative		Positive
3-plus	Negative		"
2-plus	2-plus		
2-plus	1-plus		Weakly positive
2-plus	Doubtful		" "
2-plus	Negative		" "
1-plus	1-plus		Very weakly positive
1-plus	Doubtful		" " "
1-plus	Negative		" " "
Doubtful	Doubtful		Doubtful
Doubtful	Negative		"
Negative	Negative		Negative

Method II

ANTIGEN NO. 1 CHOLESTERINIZED (ONE TUBE)	ANTIGEN NO. 2 NEXT WEAKER ANTIGEN (ONE TUBE)	INTERPRETATION
2-plus	2-plus	4-plus .... Very strongly positive
2-plus	1-plus	3-plus .... Strongly positive
2-plus	Doubtful	2-plus .... Positive
2-plus	Negative	2-plus .... "
1-plus	Doubtful	1-plus .... Weakly positive
1-plus	Negative	1-plus .... Very weakly positive
Doubtful	Negative	? .... Doubtful
Negative	Negative	– .... Negative

CONTROLS EMPLOYED IN TITRATION

1. Amboceptor for isohemolytic activity.
2. Complement for isohemolytic activity.
3. Saline for isohemolytic activity.

CONTROLS EMPLOYED IN REACTION

1. Each serum for anticomplementary property in double amount used in test.
2. Positive luetic serum.
3. Negative or normal serum.
4. Cholesterin antigen for anticomplementary property in five times amount used in test.
5. Simple alcoholic extracts and Noguchi antigens in double or triple amounts used in test.

In order to completely duplicate in preliminary titrations the conditions of the actual Wassermann test, two procedures are now followed which are not indicated in the description and protocols above. Complement is placed in the incubator for one hour before its use in titrations of the hemolytic system, and the amboceptor and cell suspensions are sensitized for one-half hour before hemolytic titrations.

A METHOD FOR PRESERVING A SHARP SCALPEL IN EXPERIMENTAL SURGERY*

By F. C. Mann, M.D., Rochester, Minn.

ONE of the problems in the mechanics of surgery is to maintain instruments in good working condition. In experimental surgery it has been found difficult to keep a good edge on scalpels, mainly due to the fact that section of the animals' skin dulls the edge of the knife. This problem is solved by obtaining a cheap knife to make all skin incisions. A high grade, all metal, small paring knife has been found to suit our purpose. These knives are made in various shapes so that almost any style can be obtained. They sharpen readily and are quite strong. As they are composed entirely of metal they withstand boiling. They usually can be used three or four times before they need to be retouched on the stone.

The present technic for making an incision is as follows: After the usual preparation, the skin and fascia are cut with one stroke of the paring knife which we term the "skin knife." The sharp, heavy blade of the knife makes a sure, clean incision possible. As soon as the skin incision is made, the knife is dropped in the pan for used instruments and after catching the bleeding points and placing the skin towels in position the rest of the incision is made with the regular scalpel. While the knife was obtained for the purpose of saving the edges of the scalpels, it also makes possible another point of technic which some surgeons hold important, namely, the use of a scalpel which has not passed through the skin for the deep part of the incision.

*From the Division of Experimental Surgery and Pathology, Mayo Clinic.

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EDITORIALS

The Negro Population

THE Census Bureau has issued a most interesting volume on the negro population of this country from 1790 to 1915, a period of 125 years. At the beginning of this period there were 757,208 negroes in this country with 239 for every 1000 of the white population. Up to 1808 the negroes were increased by importation, but the proportion to the whites has constantly decreased. Since 1910 neither immigration nor emigration has been great enough among negroes to materially affect the number and the increase has been wholly due to native births. In 1910 the number of negroes was 9,827,763 and for every 1000 whites there were 120 negroes. The percentage of increase in the succeeding decennial periods has gradually fallen from 30.5 in 1830 to 11.2 in 1910. Although the percentage increase fell off from period to period the lower percentages for the later periods represent larger absolute additions to the population.

In 1790 the negro population of Virginia numbered 305,493, making two-fifths of the total in the United States. In the same year the negroes in New York numbered 25,978, this state being sixth in the list. In 1860 Virginia still

had the lead with a negro population of 548,907 and was followed in order by Georgia, Alabama, Mississippi, and South Carolina, each of which had more than 400,000. In the census of 1870 and in each succeeding census Georgia has stood at the head of the list with a negro population in 1910 of 1,176,987. In the South as a whole 29.8 per cent of the population in 1910 was negro; in the North 1.8 per cent, and in the West 0.7 per cent. The negro proportion was highest in the South Atlantic division in which it reached 33.7 per cent. In the East South Central it was 31.5 per cent, and in West South Central 22.6 per cent. In the North the negro proportion in the population has not changed materially since 1850, and it has not at any census since that date amounted to so much as 2 per cent. In the North the percentage declined from 3.4 in 1790 to 2 in 1850. At no census has the proportion in the West amounted to more than a fraction of one per cent. Washington had in 1910 the largest negro population, while New York came second. Birmingham had the largest increase in negro population during the decade 1900-1910, with New York second. Taking the country at large, the negro is the most rural. Only 27.4 per cent of the negroes were in 1910 urban, while among native whites born of natives, the urban percentage was 36.1; of mixed parentage 59.4 per cent; of double foreign parentage 68.1 per cent; of foreign born whites 72.2 per cent. These figures indicate that the foreign element tends to possess our cities and exclude both the native white and the negro. In 1910 the negro constituted 6.3 per cent of the urban population of the United States, 28 per cent of that of the South, 2.4 per cent of that of the North and 1 per cent of that of the West. When the negro migrates from the South to the North he generally goes to a city, but the percentage of the negro urban population of the North did not increase from 1890 to 1910. This does not mean that negroes did not come from the South to the North during this twenty-year period, but such a movement was neutralized when calculated in percentage by increased white urban population in the North. In the South as a whole the percentage of negroes in the urban population decreased from 31.7 per cent in 1890 to 28 per cent in 1910, and in the rural population from 34.2 per cent in 1890 to 30.3 in 1910. There are thirty-two counties in the South which report no negroes, twenty-eight of these are in Texas, two in Oklahoma, and one each in Arkansas and North Carolina. The District of Columbia, regarded as a county, contains the greatest number of negroes; Shelby County, Tennessee, including Memphis, comes next, and Jefferson County, Ala., including Birmingham, stands third. In 1910 there were males of military age (18-44 years) 20,473,684, of which 1,985,415 were negroes and 18,351,870 whites; the latter being divided into native whites, 13,880,182 and foreign born 4,471,688.

In the period of sixty years from 1850 to 1910 the proportion of mulatto in the negro population increased from 11.2 to 20.9 per cent. In 1850 the proportion of mulatto in the free colored population greatly exceeded the proportion in the slave population, the number of mulattoes to 1000 blacks being 581 in the free and 83 in the slave population. The number of mulattoes to 1000 blacks in 1910 was 252 in the South, 363 in the North, and 473 in the West. While in round numbers one-third of the blacks are illiterate, only one-fourth of the mulattoes are unable to read and write. May we infer from these facts that the negro is to be absorbed by the white race? It seems that cohabitation is more

common now than in slave times and that the mixed race is being better educated than the original.

There are some interesting points concerning the marital state. The negro, both male and female, both urban and rural, marries at an earlier age than the white; though taking all ages, about the same per cent of the males of both races marry, while more white women than negroes marry. Widowhood is much higher among negro than among white women. There are also more divorces among negroes than whites. The tendency of negroes to marry at younger ages than the whites is clearly in evidence in the statistics for both urban and rurals. In the urban population 31.6 per cent of negro males aged 20 to 24 years as compared with 14.8 per cent of native white males of this age were married, the corresponding percentages for rural communities being 40.4 for negroes and 26.3 for native whites. Among females 20 to 24 years of age in urban communities the percentage married was 50.5 for negroes and 38.7 for native whites; the corresponding percentages in rural communities being 63.2 and 55.6. In the South among both male and female negroes the percentage single is highest in cities of 100,000 and over and lowest in the rural population.

In 1820, although the proportion of children under 14 in the negro population was approximately the same as the proportion in these ages in the white population, the number of such children per 1000 women, 14-44 years of age, in the negro population was considerably below the number in the white population. In 1910 both the proportion of children in the negro population and the proportion of children to women very considerably exceeded the corresponding proportions among whites. In both races the decline for the proportion of children under 14 for the period of 90 years from 1820 to 1910 is very marked. Among the negroes it is somewhat less than it is among whites, although it is to be noted that in the latter decades of this period for which data are available in greater detail the decrease in the number of children under five years of age per 1000 women 15 to 44 is in the aggregate somewhat greater among negroes than among whites, the result being a closer approximation of the ratio for negroes to that of whites.

It is impossible to obtain exact data on the annual death rate in the negro population. At each decennial census from 1850 to 1900 there was an attempt made to collect mortality statistics by inquiring of the living concerning those who had died during the twelve months of the census year. From the first this method of gathering mortality statistics was recognized as an absolute failure. It was a demonstration of the fact that the dead are easily and quickly forgotten. The compilers of the census of 1850 recognizing this wrote, "In regard to the number of deaths, the returns of the census are not likely to deceive anyone, since an attempt to reason from them would exhibit a degree of vitality and healthfulness in the United States unparalleled in the annals of any nation. * * * * Nothing short of a registration system in the States can give the required data satisfactorily since people will not, or can not, remember and report to the census taker the number of facts and the particulars which occur in the period of a whole year or longer prior to the time of his calling."

The states and cities are now building up the registration of births and deaths and the census maker relies on these and has ceased to trust the memory

of the living concerning either the names or numbers of the dead. Now (1919) the registration area embraces about 70 per cent of our population and covers about 50 per cent of our area, but the mass of the negro population is not in this area. Most cities in the South belong to the registration area and the states are gradually but slowly progressing in this direction. All the census maker can do is to take the annual death among negroes and whites in the registration area. In 1910 the annual death rate among all whites in this country was 14.6 per 1000, while the corresponding figure for the negro population was 25.7. In 1910 there were only four countries in the world keeping any kind of mortality statistics with a higher annual death rate than that prevalent among the negroes in our registration area. These were Ceylon (27.3) European Russia (28.9) Chile (31.1) and Mexico (33.3).

Is this high death rate among our negroes due to racial defects or to environmental conditions? Upon the true answer to this question the future of the race largely depends. Many European countries now with an annual death rate comparable with that among our whites had a generation or more ago a rate quite as high as that among our negroes now. In 1910 the death rate in Holland was 13.6; in 1860, it was 25.4. That of Germany in 1910 was 16.2; in 1885 it was 25.1. It seems therefore if the high death rate among the negro population is wholly due to environment we may expect a great improvement within a few generations.

"Although negro infant mortality in 1910 was greatly in excess of white infant mortality—the excess of the negro over the white rate being 136.9 for males and 126.7 for females—the figures for 1910 indicate marked improvement during the decade 1900-1910. In this period infant mortality among negro males declined from 380 in 1900 to 280.3 in 1910, the decrease in the rate amounting to 99.7, and the rate for negro females declined from 309.7 in 1900 to 243.2 in 1910, the decrease amounting to 66.5." There could be no better evidence of increased intelligence among negro mothers.

"Three principal causes of death in the negro population, namely, tuberculosis, pneumonia and organic diseases of the heart—are the principal causes of death also for the white population. Per 1000 deaths from all causes in 1913, in the negro population, 366 or more than one third, and in the white population, 291 are classified under one or other of these three causes."

However, tuberculosis is much more prevalent in the negro population than in the white, being 176 to 98. In the white population pneumonia and organic diseases of the heart are nearly of equal importance with tuberculosis as causes of death, the number of deaths from these two causes per 1000 deaths from all causes being 94 to 99 respectively. In the negro population these causes are relatively to other causes much less prevalent than tuberculosis, the number per 1000 deaths from all causes in the negro population being for pneumonia 100 and for organic diseases of the heart 90.

"Tuberculosis developed a rate per 100,000 population in 1910 of 463 among negroes, which was more than three times the tuberculosis rate of 148 per 100,000 white population. The rate for pneumonia was 298 or more than twice the pneumonia rate of 142 among whites. The rate for organic diseases of the heart was 212 among negroes and 139 among whites." It appears from these

figures that each of these three diseases is either more prevalent or more fatal, or both more prevalent and more fatal among negroes than among whites. Is this due to greater susceptibility on the part of the negro or to living conditions? So far as pneumonia is concerned, the evidence gathered from the army camps indicates that there is not a marked difference between the southern white and the southern black and both are more susceptible to this disease than their comrades of either color from the North. Under ordinary conditions army statistics show that pneumonia is more deadly the farther South one goes. This was doubtful, however, with post influenza pneumonia.

We are inclined to advance a tentative opinion that the higher death rates from tuberculosis and pneumonia among the blacks are due to living conditions while the higher death rate from heart disease is due to the wider prevalence of syphilis among the blacks. However, this point needs more careful study.

The diseases more prevalent among whites are cancer— with an annual rate of 57 among negroes and 77 among whites per 100,000 population—diphtheria, measles, diabetes, and cirrhosis of the liver.

So far as school attendance is concerned, the writer of the report before us makes the following statement: "Reviewing the situation as a whole, while it is true that the proportion of negro children not in school is large, not only in rural communities but even in large cities; and although in the South, the proportion of negroes not in school greatly exceeds the corresponding proportion of whites, still the data for school attendance presented establishes the fact of rapid improvement in the condition of negroes in the South. * * * * Should the next census show a similar advance the negro race in its school attendance will not stand far behind the white."

Taking all inhabitants over ten years of age the percentage of illiteracy among negroes was in 1910, 30.4; among whites 5.0. Taking all between ten and fourteen, the figures for the blacks are 18.9, for the whites 1.8. In 1890, 39.8 per cent of the negro population ten to fourteen years of age were illiterate; in 1900, 30.1 per cent, and in 1910, 18.9 per cent. Of course the percentage of negroes who attain anything more than an elementary education remains small.

In criminality the negro makes a bad showing and he behaves far worse in the North than in the South. The following excerpts illustrate: "30.6 per cent of the total number of prisoners and juvenile delinquents enumerated on January 1, 1910, and 21.9 per cent of the total number committed during the year 1910 were negroes, whereas the percentage of negroes in the total population was only 10.7. Per 100,000 negro population the number of negro prisoners and juvenile delinquents enumerated on January 1st was 424.6 and the number committed during the year 1101.7, the ratios for negroes being markedly in excess of the corresponding ratios shown for whites. * * * * They represented 56 per cent of the total number committed for grave homicide, 49 per cent of the total for lesser homicide, and 41.1 per cent of the total for assault. They contributed 33.6 per cent, or one-third the commitments for prostitution and fornication, and almost as large a proportion of the commitments for robbery, burglary, and for violating liquor laws. On the other hand they comprised only about 16 per cent of those committed for drunkenness and disorderly conduct and for vagrancy." In the North the serious offenses committed by the negro are arranged in the

order of frequency as follows: (1) grave homicide, (2) prostitution and fornication, (3) lesser homicide, (4) robbery, (5) assault. In the South they are as follows: (1) assault, (2) grave homicide, (3) larceny, (4) robbery, (5) burglary. The ratio of commitments as between blacks and whites is from two to three times as high in the North as in the South. This means either that the southerner is more lenient with the negro or that the negro behaves better in the South.

The compilers of the report make statements concerning the relative prevalence of insanity in the two races with caution. The figures are based on the number admitted to and in asylums during the census year. "Negroes constituted 6.9 per cent of the insane enumerated at the beginning of the year and 7.2 per cent of the insane admitted during the year. The percentage of negro insane was accordingly very considerably below the percentage of negroes in the population (10.7). For negroes the ratio of inmates present on January 1st per 100,000 negro population was 131.4, the corresponding figures for whites being 213.2. The ratio of admission per 100,000 population was 44.6 for negroes and 68.7 for whites. These ratios did not, however, obtain with any degree of uniformity in the several geographical divisions and states. Outside the South the ratio for negroes was in fact higher than that of the whites in each division. In New England, for instance, the ratio per 100,000 population for inmates enumerated on January 1st was 473.6 among negroes and 296.9 among whites, the corresponding figures for admissions being 153.8 for negroes and 105.9 for whites."

The conclusion seemingly justified by these statements is that the negro in the North is more prone to insanity than his brother in the South, or the southern negro, though insane, is less frequently sent to asylum.

There are no trustworthy statistics concerning the feeble-minded.

The number returned as blind per 100,000 negro population was 90, the corresponding proportion for whites being 58.2 per 100,000. This is most certainly due to the greater prevalence of gonorrhea among the blacks.

"The figures rather confirm the supposition that deaf-mutism is less common among negroes than among whites." The compilers of the census attribute this to the lighter prevalence of measles, scarlet fever and diphtheria among negroes and say: "While the death rate from measles in 1914 was only slightly higher for whites than for negroes, the death rate from diphtheria was nearly twice as great and that for scarlet fever was practically four times as great for whites as for negroes. On the other hand, negroes appear to be somewhat more susceptible to meningitis, another leading cause of deaf-mutism, than are whites."

Counting as paupers those sent to and maintained in almshouses, the negro slightly outnumbers the native white in the South; in the North he doubles the native white; while in all sections of the country the foreign-born white exceeds the combined strength of his competitors.

In regard to the ownership of homes the census enumerators were instructed as follows: "A home is to be classed as owned if it is owned wholly or in part by the head of the family living in the house. It is not necessary that full payment of the property should have been made."

"Every house not owned either wholly or in part by the family living in it should be classed as rented whether rent is actually paid or not."

Owned homes are divided into free owned and mortgaged.

With the above understanding, owned homes increased from 18.7 per cent of all negro homes in 1890 to 21.7 per cent in 1900, to 23.3 per cent in 1910.

The percentage of free owned homes slightly decreased during the decade 1900 to 1910. "This decline was not due to any decrease in the number of free owned homes—the number owned free, both of farm houses and of other houses, increasing in this decade as in the decade following—but to a relatively more rapid increase in the number of homes owned under a mortgage or other lien. Such ownership is undoubtedly in many cases a first step out of tenancy."

"Of negro farm homes 98.5 per cent were in the South in 1910, 1.4 per cent in the North and 0.1 per cent in the West."

"The term 'family' as defined for census enumeration means a group of persons whether related by blood or not who live together as one household, usually sharing the same table."

As thus defined the negro family averaged exactly the same number as the whites in 1910 (4.5). This gives us no information concerning housing conditions. There may be several families in one house.

"In the negro population, both male and female, the proportion gainfully employed increased in each of the last two decades, among males from 79.4 per cent in 1890 to 84.1 in 1900, and to 87.4 per cent in 1910; and among females from 36.2 per cent in 1890 to 40.7 per cent in 1900, and to 54.7 per cent in 1910." Taking the whole negro population over ten years of age in the country 29 per cent were not gainfully employed in 1910. Of the male negro population ten years of age and over in the South, 56.6 per cent were engaged in agricultural and 31.1 per cent in nonagricultural pursuits, the percentages for females being 32.4 and 23.5. In the North and West 75.7 per cent of the negro males and 45.1 per cent of the females were engaged in nonagricultural pursuits; the proportion engaged in agricultural pursuits being 10.1 per cent for males and 0.4 per cent for females, and the proportion not gainfully employed 14.2 for males and 54.5 per cent for females.

More than one-third of the total negro women returned as gainfully employed in 1910 were returned in two occupational groups, as either "servants" or "laundresses not in laundries."

In 1910 negroes made up 14 per cent of all farmers in the country. In many of the mountain and Pacific states and even in New York, Wisconsin, Minnesota, North Dakota, South Dakota, and Nebraska other colored men, Indians, Chinese and Japanese outnumber the negro farmers. More than 60 per cent of the farmers of Mississippi are negroes, between 50 and 60 per cent in South Carolina, and between 40 and 50 per cent in Georgia, Alabama, and Louisiana. In the decade from 1900 to 1910 the value of farm property operated by negroes more than doubled.

As valuable as this report is, there are many questions about the negro left unanswered. In considering the welfare of the nation this race can not be left out of consideration. It is regrettable that he was brought here, but he was not consulted on this point and now that he is here to the number of about one-

tenth of the population, what is to be his future and what effect is he to have on the future of the white race? In making a forecast on these points the census compilation is of the greatest value, but we should like to know more. Absorption by the white race, indicated by increase in the number of mulattoes is a most interesting matter. We would like to know how the mulatto compares with the pure stock physically, mentally, and morally. Most biologists agree that for the betterment of the race two fundamental conditions are desirable: (1) Father and mother must not be too much alike, (2) Father and mother must not be too much unlike. For the first reason cousins of the first degree must not marry. As a consequence of the second law, we point to the mixed races of India, South and Central America and we conclude that the mongrel inherits the bad traits on both sides of the house. Does the mulatto comply with or violate this rule? Possibly in a later census more light on this point may be secured, but whatever the answer to this question may be it seems certain that the mulatto will multiply and one thousand years from now, if the world last so long, the black negro in this country will be as rare as a white elephant. In the meantime it seems quite evident that the mass of the race will remain in the South where there will be more or less segregation. In all probability the death rate will fall with improved sanitation and increased knowledge. In our opinion the most difficult medical problem in attempting to improve the race is that of the venereal diseases. Army statistics have shown for the first time the alarming prevalence of syphilis among the blacks. It is bad enough among whites, but among the blacks it is untreated and unless improvement be made, a few more generations may materially reduce the numbers. From the increase in mulattoes it is evident that syphilis among the blacks constitutes a serious menace to the whites as well.

V. C. V.

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ORIGINAL ARTICLES

COMMUNICABLE DISEASE IN THE UNITED STATES ARMY DURING THE SUMMER AND AUTUMN OF 1918.*

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PREFACE

THE following report on communicable disease in the army is based on the weekly telegraphic reports sent in to the Surgeon General from each camp, post, and army station, and upon the special reports made by division and camp surgeons, epidemiologists and others. The data are the most accurate obtainable at the time. We have observed a lack of agreement in reports from the same camp. The disagreements we have tried to fathom and eliminate and believe we have done so in the great majority of cases.

Before the complete truth about sickness in the army is known, it is necessary to analyze the records which eventually will reach the Surgeon General on the sick and wounded cards. Their compilation is a time-consuming task. In the meantime we are presenting this exposition of facts obtained from another angle, but whose interpretation we do not expect to see altered in any material degree by later analyses.

We desire to state that Major Alfred E. Shipley worked with us for nearly three months in the compilation of this report and we owe much to his counsel, advice, and help.

During a great part of the time this study has proceeded under the direction and with the kindly assistance of Lt. Col. George R. Callender.

*A report from the Section of Communicable Diseases, Division of Laboratories and Infectious Disease, prepared under the direction of Col. Frederick F. Russell, and published by permission of the Surgeon General. The writers are printing this as a preliminary report, subject to revision on the receipt of further data and will be grateful to all medical officers for more exact information on matters which came under their observation. Part II will be published in the August issue of this Journal.

We desire to thank division and camp surgeons, epidemiologists and other medical officers for the basic material of this report. Valuable data have been supplied by the United States Public Health Service, the Census Bureau, the Medical Bureau of the Navy, state and municipal health commissioners.

The tables and illustrations have largely been executed and owe their excellence to Hospital Sergeants Alvin D. Stultz and Edward H. Maitlen.

Section I

Introduction

The wise enactment and admirable execution of the draft law demonstrated that a great Democracy could mobilize, equip and place in the field, 3000 miles across the sea, an army efficient in battle. During the recent war our country prepared for service nearly four million men. They came, for the most part, not only willingly but eagerly, from farm, village and city. The university graduate and the illiterate, the poor and the rich, skilled and unskilled donned the khaki and began preparations for the task which they accomplished with speed and satisfaction. To care for the health of these men, to restrict the spread of disease among them, to restore so far as possible the sick and wounded to health has been the function of the medical department of the army. The task has fallen on us to tell to what extent and in what manner this work has been done.

Camps and cantonments for the reception and training of raw recruits came into being during the summer of 1917. The history of communicable disease in the army during the six winter months, October, 1917, to March, 1918, was prepared by the present authors, and published in the August, 1918, issue of the *Journal of Laboratory and Clinical Medicine* and reproduced in the September and October issues of the *Military Surgeon*. The purpose of the present contribution is to take up the account in April, 1918, and to carry it to the end of that year.

The procedure followed in the mobilization of our troops was not exactly that which would have been recommended by a board of sanitarians. This statement is made not with any thought of criticism. As hinted above, the draft law in itself, the execution of its provisions, and the results attained, will always be regarded as one of the greatest of our national achievements. The purpose of the mobilization was to assemble young civilians and to convert them into efficient soldiers in the shortest possible time, and was not to make a national demonstration in preventive medicine. In evaluating the results attained by the medical officer, the conditions under which he has been compelled to work must be duly considered. In this instance, both the soldiers and the medical officers, who were to have charge of their health, existed only in embryo, so far as military function is concerned when mobilization began. The hasty assembling of young men from every part of the country in groups of 27,000 or more brought into each camp practically every infection existent in the country among individuals of the same age group. The drafted men from each state were assembled at one or more points and held until a certain number had accumulated and then sent by troop trains to a designated camp. The

time covered in assembling and transferring varied from a few hours to as many days. It is reported by the camp surgeon at Wheeler that every troop train that reached that camp in the fall of 1917 brought from one to six cases of fully developed measles. In April, 1918, a colored draft contingent was assembled in Alabama and sent by troop train to Camp Custer, Michigan. On arrival, many cases of pneumonia were sent from this contingent directly to the base hospital at Custer. The coming of these troops not only increased the morbidity from pneumonia at Custer, but introduced a new type of the disease. This occurred frequently and at different camps. The control of epidemics under such conditions is a far different matter from that which concerns the local health authorities in a comparatively stable population.

For the convenience of our readers, we offer the following summary of the findings reached in our report on communicable disease during the winter of 1917-18:

1. Measles was nineteen times as prevalent in our training camps as in civilian life. The undue prevalence of this disease was especially noticeable in those camps which drew a large portion of their troops from rural populations. Organizations from the larger cities showed no more measles than appeared in the same age group in the cities from which they came. The number of cases in the different camps was determined by the number of susceptibles. Epidemics of this disease ceased when the susceptible material had been exhausted and reappeared when the spark and the inflammable substance were brought together. We fail to find convincing proof that any precautions taken limited the spread of this disease. Some of these measures may have retarded its spread, but none completely arrested it.

2. The pneumonias were twelve times as prevalent in the camps as in the civilian population. Again it was the rural and southern soldier who suffered most severely during the winter of 1917-18. However, in every camp the morbidity from this disease was higher than it was in the same age group at home. During the time covered by our report the morbidity from the pneumonias varied widely in the camps and these variations were apparently not influenced by the location of the camp but by the part of the country from which the troops came. Northern and urban men suffered least; southern and rural men most.

3. Meningitis was forty-five times more prevalent in the camps than in the civilian population. While no camp escaped this infection, it prevailed alarmingly in only three and these were camps which drew their troops from areas in which this disease was at the time endemic. These camps were Jackson, S. C., Beauregard, La., and Funston, Kan.

4. Scarlet fever was six times as prevalent in the camps as in civil life. Two camps, Beauregard, La., and Wheeler, Ga., had no cases of this disease. Pike, Ark., had the largest number and it may be well to remark that about one third of the troops in this camp were from the North. Apart from Pike, there was more scarlet fever during the winter months of 1917-18 among troops from the North and West than among those from the South. However, we are not justified in drawing any general conclusion from this fact.

5. Diphtheria was twice as prevalent in the camps as in civil life. Deaths

from this disease occurred in seven of the 29 camps whose records were studied. The annual death rates per 100,000 in these were as follows:

Pike	30
Funston	22
Dodge	18
Cody	17
Custer	10
Doniphan	8
Logan	7

The rate in the registration area in 1915 for all ages was 15.7.

6. Tuberculosis was thirteen times more prevalent among civilians than among soldiers. This is due to the elimination of the tuberculous in the examinations of the drafted men. That there were deaths from this disease during the first six months after mobilization indicates that some of the examiners were not skillful in the detection of this disease even in moderately advanced stages. At Camp Wheeler the annual death rate for this disease during the winter months of 1917-18 was 80 per 100,000, which is but slightly below that of the total population of Michigan without any examination or selection.

7. Typhoid fever and its allied diseases, including dysentery, were negligible, the annual death rate among all troops in the United States for the six winter months of 1917-18 being 1.3, while that for the state of Delaware for the same period was 55. It may be worthy of note that vaccination for this disease as practiced in the army gives protection against ordinary doses of infection, but the protective effects may be overcome by massive infection.

8. The following figures show the relative death rates from all causes in the army and in civilian life. The army rate is computed for the six winter months of 1917-18, while the civil rate is that of the corresponding months of 1915-16.

Place	Annual Death Rate per 1000
Army	9.1
U. S. Registration Area	
All Ages	14.3
Age 20-49	8.3
Age 20-39	6.8
Age 20-29	5.7

In the present article the time from April to December, 1918, is divided into two parts for statistical treatment. This is done in order to set forth the seasonal influence on disease. Ordinarily we should have grouped together the months from April to September inclusive, calling this the "summer season" as contrasted with the months from October to March inclusive, which was regarded as the "winter season." However, the occurrence of the influenza epidemic in September and the following months has caused us to alter this grouping and treat as the "summer season" the period from April to August inclusive. The four remaining months of 1918 are then treated under the term "autumn season."

The annual death rate per 1000 for the summer season was 5.7, practically the same as that of civilians in the age of group 20 to 29 years during the six winter months. For the corresponding five summer months of the year 1916, the death rate from all causes for this age group in civilian life is estimated to be 4.6. Consequently, the low rate of 5.7 of the army is still a trifle above

that of civilian life. This is a remarkable showing, for although the army is composed of young men selected on account of superior physical make-up and men who might be expected to have a lower death rate than the average among those of their own age, still, when we consider the hazard that is always associated with the mobilization of very large numbers for military service, the rate of 5.7 for the summer season may be pointed to with pardonable pride.

During the summer season pneumonia continued to be the chief cause of death. However, the greater part of this fatality occurred during the months of April and May. Contrary to the experience of the previous winter, the pneumonias prevailed more extensively in the middle western camps than elsewhere. In many camps measles was present but to a far less extent than during the winter period. The prevalence of this disease during this period was undoubtedly dependent upon the number of susceptibles in the camp. During the winter months, Wheeler stood third in measles incidence while in March there were no cases in this camp. During the winter, Wheeler had been so permeated with this disease that every susceptible individual was affected, and then the diseased ceased. There were no new men added to Wheeler until autumn, and susceptible material for the continuation of measles was lacking.

In discussing typhoid fever in our previous report, we stated that the low typhoid rate at that time might in part be attributed to the fact that the winter season was not the typhoid period of the year and the real test of preventive inoculation would come during the summer. It was the summer season which witnessed the typhoid scourge in 1898. Now that we have passed through the summer of 1918 and have experienced a typhoid death rate but little greater than that of the preceding winter, we can rest quite comfortably in the conclusion that the control of this and its allied diseases is within the power of man. The annual typhoid death rate per 100,000 during the summer season was 3.3, but these figures do not do justice to the preventive measures employed, for many of the cases that did occur were among men who had contracted the infection prior to receiving their vaccination.

Malaria, another warm season disease, increased during the summer to a slight degree only. For the most part, malarial admissions to the hospital were among men who had the infection prior to entering service. Although some of the camps were in malarial districts, there is no evidence that any number of infections originated in these camps.

Coming now to the "autumn season," counting September to December inclusive, we find ourselves facing a wholly different condition. During this period the unparalleled pandemic of influenza reached and spread to the remotest parts of this country. Among our soldiers the death rate rose from 5.7, that of the summer season, to 48.5 for the autumn season, an increase of nearly tenfold. Still more impressive is the actual number of deaths. During these four months there occurred in the various army camps in this country 23,712 deaths, no less than 94 per cent of which was due to influenza and complicating pneumonia. This means that 1.5 per cent of the military forces was effectually eliminated in the infancy of their career.

Out of nearly four million men who passed through the army camps of this country from September, 1917, to January, 1919, 30,859 have died from disease

before reaching the port of embarkation. Up to November 26, 1918, 16,000 of our soldiers in France died of disease. This makes a total of 47,000 American soldiers who gave up their lives in our hospitals, serving their country less conspicuously, but none the less heroically, than those who died on the fields of battle. Of the two million men landed in France, 40,000 perished in combat according to Pershing's report dated Nov. 26, 1918. Of the total 87,000 deaths, 54 per cent was from disease. As war records go, this is not an unusual showing. Of the deaths in our Civil War among northern troops, 66 per cent was from disease; in the Franco-Prussian War, the French Army, 68 per cent, German Army 31 per cent; in the Spanish-American War, United States Army, 84 per cent; in the Russo-Japanese War, Japanese Army 32 per cent, Russian Army, 29 per cent. In the American Expeditionary Force the percentage dying from disease up to November 26, 1918, was 29.

Preventive medicine is making rapid progress. Malaria and typhoid fever, once the scourges of armies, are well in hand. Typhus is no longer an enigma, but still requires close watching. The pneumonias remain and constitute at present the greatest cause of death in all armies. Protective inoculation against the pneumonias has been tried only recently, and the results are promising. The combination of influenza and pneumonia has been most distressing and disastrous both in military and in civilian populations. During the autumn season of 1918, civilian communities suffered greatly, but on account of the high concentration of susceptible material in our camps, the death rate among soldiers has been higher than among civilians. No part of the world has escaped this great scourge. In the past, there have been pandemics, but none, so far as we have statistical evidence, has wrought such heavy destruction as this. Hitherto the pandemic of 1889-90 has been looked upon as the most widespread and probably the most fatal. At that time more than 40 per cent of the population of Massachusetts was affected, but the death rate was not so high. The pandemic of 1918, when compared with that of 1889-90 is estimated to have caused *six times as many deaths.*

During the four autumn months of 1918, 338,343 cases of influenza were reported to the Surgeon General. This means that in the camps of this country *one out of every four men had influenza.*

The combination between influenza and pneumonia during the fall of 1918 seems to have been closer and more destructive than in any previous pandemic. During the autumn season there were reported to the Surgeon General 61,691 cases of pneumonia. This means that *one out of every twenty-four men encamped in this country had pneumonia.*

During the same period 22,186 men were reported to have died from the combined effects of influenza and pneumonia. This means that among the troops in this country *one out of every sixty-seven died.*

This fatality has been unparalleled in recent times. The influenza epidemic of 1918 ranks well up with the epidemics famous in history. Epidemiologists have regarded the dissemination of cholera from the Broad Street Well in London as a catastrophe. The typhoid epidemic of Plymouth, Pa., of 1885, is another illustration of the damage that can be done by epidemic disease once let loose. Yet the accompanying table shows that the fatality from influenza and

pneumonia at Camp Sherman was greater than either of these. (See Table 1 and Chart 1). Compared with epidemics for which we have fairly accurate statistics, the death rate at Camp Sherman in the fall of 1918 is surpassed only by that of plague in London in 1665 and that of yellow fever in Philadelphia in 1793.

The plague killed 14 per cent of London's population in seven months' time.

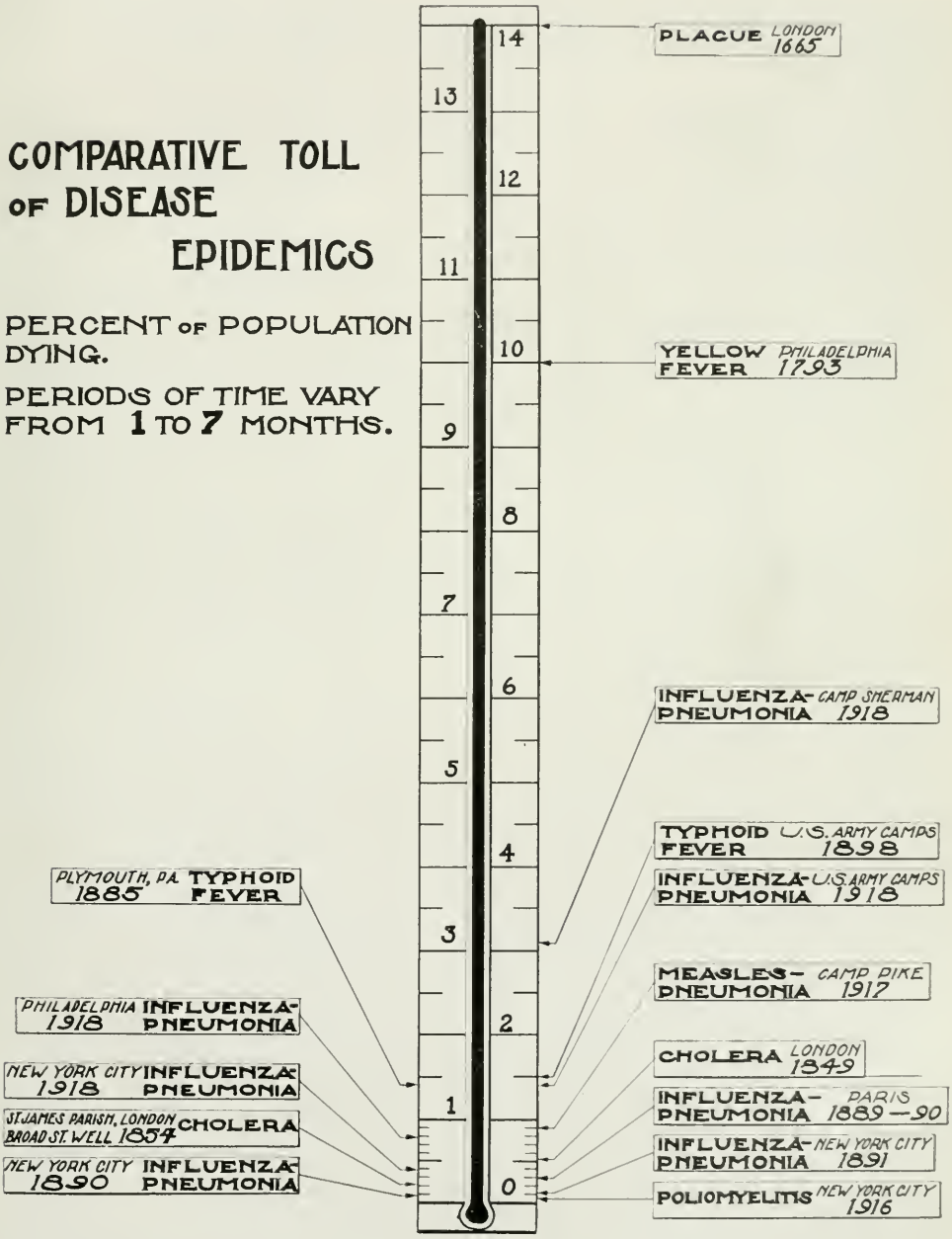


Chart I.

Table 1

Comparative Toll of Disease Epidemics

	DISEASE	PLACE	YEAR	PERIOD	POPULATION	DEATHS DURING PERIOD	% POPULATION KILLED DURING PERIOD	% POPULATION KILLED PER MONTH
1	Plague	London	1665	7 months	500,000	68,593	14.	2.0
2	Yellow fever	Philadelphia	1793	4 months	40,100	4,041	10.	2.5
3	Influenza-pneumonia	Camp Sherman	1918	7 weeks	35,100	1,073	3.1	1.9
4	Typhoid fever	U. S. Army Camps	1898	4 months	108.000	1,580	1.5	.38
5	Influenza-pneumonia	U. S. Army Camps	1918	4 months	1,500,000	21,500	1.4	.35
6	Typhoid fever	Plymouth, Pa.	1885	1 month	8,000	114	1.4	1.4
7	Measles-pneumonia*	Camp Pike	1917	14 weeks	28,100	252	.90	.28
8	Influenza-pneumonia*	Philadelphia	1918	7 weeks	1,761,000	13,500	.77	.48
9	Cholera	London	1849	23 weeks	—	—	.51	.096
10	Influenza-pneumonia*	New York City	1918	7 weeks	5,740,000	14,700	.3⁹	.24
11	Influenza-pneumonia*	Paris	1889-1890	7 weeks	2,260,000	6,500	.29	.18
12	Cholera	St. James Parish, London ("Broad St. Well")	1854	17 weeks	318,000	700	.22	.056
13	Influenza-pneumonia*	New York City	1891	1 month	1,681,000	1,818	.11	.11
14	Influenza-pneumonia*	New York City	1890	1 month	1,631,000	1,370	.08-	.084
15	Poliomyelitis	New York City	1916	5 months	5,602,000	2,407	.043	.009

*Mortality computed indirectly from excess deaths from all causes above norm.

Yellow fever destroyed 10 per cent of the population of Philadelphia in four months. In seven weeks influenza and pneumonia killed 3.1 per cent of the strength at Camp Sherman. If we consider the time factor, these three instances are not unlike in their lethality. The plague killed 2 per cent of the population in a month, yellow fever 2.5 per cent and influenza and pneumonia 1.9 per cent.

In four months typhoid fever killed 1.5 per cent of the soldiers encamped in this country during the war with Spain. Influenza and pneumonia killed 1.4 per cent of the soldiers in our camps in 1918 and it also covered a period of four months.

During the winter of 1917-18, Camp Pike showed the highest death rate of the larger camps, this being due for the most part to pneumonia to some extent following measles. In fourteen weeks Pike lost 0.9 per cent of its strength. This is about one-third of Sherman's loss but the deaths at Sherman occurred in one-half the time. In the winter of 1917-18, Camp Beauregard showed the highest weekly incidence for measles. It amounted to an annual admission rate per 1000 of 2,700. In the fall of 1918 Beauregard had an influenza admission rate during one week of 15,000. The two epidemic periods at Beauregard have been

contrasted graphically in Chart II. The 1917 epidemic looks insignificant compared to that of 1918, and yet at the time it was regarded with grave concern. Philadelphia headed the large cities in influenza fatality in this country, losing 0.8 per cent of its population. This is about one-fourth of the loss at Sherman.

The pandemic of influenza in 1918 seems to have been more closely associated with the pneumonias than appears in any previous pandemic. From

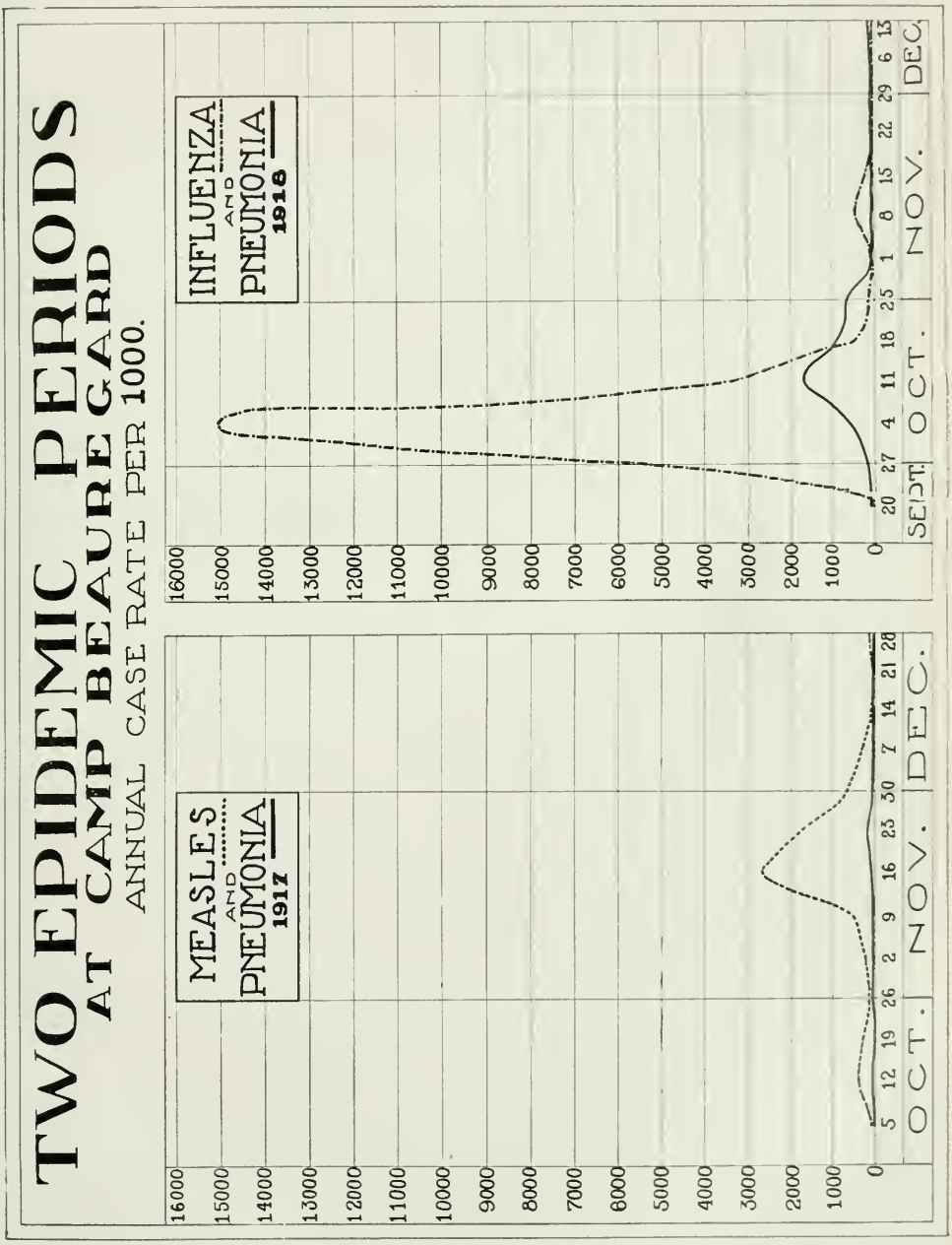


Chart II.

the reports as sent to the Surgeon General's Office, it appears that uncomplicated influenza was not by any means a fatal disease and that the high death rate was due to the pneumonias which followed. Pneumonia is a serious disease at all times. Recent records for the United States Army show that the case mortality rate for this disease has been as follows during the different periods of the last two years:

The year 1917	11.2%
6 winter months, 1917-18	23.1%
5 summer months, 1918	18.8%
4 autumn months, 1918 (influenza period)	34.4%

It is not strange that once pneumonia secured a foothold in patients already weakened by influenza their chances of recovery were lessened.

In 1893 a German bacteriologist, Pfeiffer, announced his discovery of the bacillus which has since borne his name and which he believed to be the specific cause of influenza. In this country Pfeiffer's claims have never been universally accepted. We will have more to say on this point from time to time as the evidence unfolds itself.

The pneumococcus has been long regarded as the chief cause of pneumonia. Of this organism four distinct types are recognized in this country. The fourth type is in reality a heterogeneous group which includes many organisms which may cause pneumonia and yet whose agglutinations and other reactions have not been recognized with a sufficient degree of accuracy to be accepted as a means of identification. During the past year, it has been impressed upon us more forcibly than before that other oganisms than the pneumococcus may cause clinical pneumonia. The streptococcus and the staphylococcus, at least certain varieties of these organisms, have produced clinical pneumonia in our camps. One reading the reports that have been sent in from army camps in all parts of the country is impressed by the lack of agreement as to the bacteriology which has been responsible both for influenza and the accompanying pneumonia. So far as influenza is concerned, the descriptions of the clinical symptoms agree. There is no question but that the same disease clinically has existed in Massachusetts, Kansas and California. In one place, however, the Pfeiffer bacillus, in another the streptococcus hemolyticus and in a third some form of the pneumococcus has been believed to be the cause of the disease. Suspicion has also been cast upon various strains of streptococcus, the micrococcus catarrhalis and the staphylococcus. In one laboratory there has been no difficulty in isolating the Pfeiffer bacillus from the throats of influenza patients; in another this organism has not been found and good reason is furnished to support the belief that the disease is of purely streptococcic origin. These differences of opinion with respect to the initial cause of the infection have existed to a like degree in the case of the pneumococcic organisms which have been recovered from the throats of the sick. One camp reports more of one type of pneumococcus than another. There is agreement merely in the excessive numbers of Type IV, but we must remember that this is only a "waste basket" group. Pneumococci which do not respond to reactions characteristic of Types I, II, or III are placed in group four. It follows, therefore, that the

information that type four has prevailed during the epidemic is not altogether satisfactory.

In the face of these contradictory reports, not only from army camps, but from civilian laboratories as well, we are handicapped in determining the true cause of the disease. Basing our opinion on the information which is given in detail in the pages to follow, we make the following tentative statement:

1. Influenza is an acute, highly infectious disease of unknown origin, characterized by the production of a marked leucopenia which results in withdrawal of the natural defenses of the body and the opening up of the paths of invasions for other pathogenic organisms which may be present.

2. We are of the opinion that one reason for the variation in the manifestations and course of the disease in different communities has been due to difference in the combinations of organisms which have worked symbiotically with the specific cause of influenza. This accounts for the finding of one organism prevalent in one place and another organism dominant in another.

3. We are of the opinion that the epidemic of influenza which occurred in the fall of 1918 was not a new entity but a recurrence or reappearance in a more virulent form of the disease which had prevailed in the various Army Camps during the previous year. Our justification for this statement is that there are many incidents of people who largely escaped the disease in the fall and who had experienced or lived through a similar but much milder epidemic during the previous spring. In other words, we may say the soldiers who had clinical influenza in camp prior to August and those who, although having no clinical manifestations of the disease, lived through such an epidemic, were less gravely affected when the more virulent organisms reached them in the fall.

4. We believe that the largest single factor influencing the spread of influenza is the susceptibility of the individuals among whom it has been introduced. If these individuals have been once attacked by the disease even in a mild form or lived through a mild epidemic without showing clinical symptoms, they suffer less when the disease is again introduced. Among communities not previously exposed to influenza, this disease has usually involved from 20 to 50 per cent of the personnel. The exact number affected is determined by the number of people who are naturally immune or have secured immunity by previous exposure.

5. It appears that natural immunity gives way before exposure, overwork and fatigue, as was demonstrated years ago by Pasteur in his experiments on birds with anthrax. Likewise, it is possible for human beings to have their resistance lowered by exposure to unaccustomed environment so that although naturally immune, the standard of immunity is reduced to the point where the influenza virus gains admittance, and overcomes the lowered resistance.

6. We believe that not only the rapidity with which the disease spreads, but its virulence is in direct proportion to the density of the susceptible population. In communities such as army camps and large cities, the contact of individuals is so close and so intimate that even though extra precautions are taken it is quite impossible to prevent disease from ultimately reaching all persons. Precautions such as quarantine, spreading out of the personnel, closing places of assembly, delay the progress of the disease but fail to wholly prevent it.

At present and with the data at hand we can not go further with reference to the causation and diffusion of the pandemic. In this paper it is our province to describe the spread of the disease through the army camps and to interpret the significance and conditions of its distribution, with the ultimate aim of suggesting measures which may be of value in the future in combat with the same disease.

Influenza and pneumonia so far surpassed other diseases during the autumn season that they overshadowed all others. It was expected that on account of seasonal change and the assembling of many susceptibles during the fall, measles would again become an immediate factor among the communicable diseases in our camps. In fact, there was no such outburst of this disease as occurred during the previous fall. Without exaggeration it may be said that for the time being, at least, influenza and pneumonia suppressed other infectious diseases. Typhoid fever increased to a barely noticeable degree. The death rate from this disease was somewhat higher, but the total number is so small as to barely warrant comment and not to justify any definite conclusion. Scarlet fever and malaria were both lower than during the summer. In fact there was but one scarlet fever outbreak of any importance and that occurred at Camp Hancock. Within two weeks over 300 cases were reported and this marks the largest scarlet fever epidemic that occurred in the camps in this country at any time. Meningitis increased although it did not reach the prevalence of the previous winter. The weekly incidence curve for all troops in this country, as will be shown in Section II, suggests that meningitis was in some instances a sequela to influenza. The greatest meningitis incidence corresponds with the influenza peak. Diphtheria showed no material increase. Deaths from tuberculosis were higher in the autumn than in the two previous periods, the death rate rising from 18 per 100,000 during the summer to 46 in the autumn. The rate for the previous winter was 15. The most plausible explanation for this increase in deaths is that dormant and incipient cases introduced into the army during the preceding year had accumulated and possibly were hastened into the acute stage both by the duties of camp life and by the prevalence of the epidemic of influenza and pneumonia. Quite naturally there had been from the time of the first assembling of troops an accumulation of tuberculous individuals, inasmuch as such men were not discharged but were kept in the army and under governmental control and provision.

Looking back over the years 1917 and 1918, we are deeply impressed with the influence of immunity in governing the spread of infectious diseases. Apparently measles is a very specific disease, one attack immunizing an individual for a lifetime, and there is no other process so far as we can see by which immunity to this disease may be secured. Introduce measles among a susceptible population to which it has been a stranger and it will burst forth and spread rapidly. This is what happened in the fall of 1917. On the other hand, meningitis is a disease to which a large portion of the population is naturally immune. It is a striking fact that in the army camp meningitis has not shown marked effects of contact infection. Where cases have occurred they have been for the most part, at least, sporadic and apparently without connection. This phenomenon has been observed throughout the seasons. As the rural population is

more susceptible to measles on account of lack of previous exposure, the same is true of pneumonia to a certain degree at least. In our camps it is the rural rather than the urban man who contracts pneumonia. The latter is immune largely not because he has had pneumonia, but because he has been brought frequently in contact with pneumonia causing organisms and this slight but repeated inoculation has given him a certain degree of immunity. Whereas the rural man is normally more susceptible to the pneumonias when brought in contact with the organisms causing these diseases, his susceptibility may be increased still further by such environmental factors as the weather and fatigue. The proof of this has been amply demonstrated in the numerous cases where organizations have been shifted from one camp to another. A journey by troop train has almost invariably resulted in wide inoculation and the development of a common salivary flora. Incidences of this kind will be in evidence as we develop camp histories. Men who were apparently well when starting out have been taken off the train sick and immediately transferred to the hospital. There are not isolated instances of this, but it is a common experience. The influence of travel and fatigue in lowering resistance is applicable to both urban and rural men, but is more noticeable in the latter because their susceptibility is greater to start with.

A general summary of the occurrence, dissemination and methods employed in the various camps to control disease will be given later. It is sufficient to say in this introductory paragraph that the diseases which have prevailed among our troops have been for the most part inevitable on account of our ignorance of their etiology and the methods necessary for their prevention. Along these lines there is a need for a vast amount of experimental work. We may hope that this will be done and information obtained which will enable us, should similar conditions arise in the future, to know how best to proceed to mobilize a great army and at the same time preserve the men from death by sickness. At present the most encouraging field in which to look for this knowledge is to be found in that of preventive inoculation. The success attained with smallpox, typhoid, diphtheria and tetanus points the way. It is to be hoped that the pneumonias will yield to like procedures. It remains for the bacteriologist to press vigorously his inquiries into the etiology and epidemiology of the respiratory diseases, especially the pneumonias, influenza, scarlet fever and measles. When the viruses of these diseases have been definitely identified and the avenues by which they are disseminated are discovered, it will be possible to still further greatly reduce the deaths from sickness not only in military but in civilian life.

Section II

Death and Disease in the Army as a Whole

A. Causes of Death

We have pointed out in our published review of disease in the army for the six winter months, October, 1917, to March, 1918, inclusive, that diseases of the respiratory tract caused the greatest number of deaths. Of the respiratory diseases pneumonia stands above all others. During the winter period in question, respiratory diseases, which were interpreted to cover meningitis, pneumonia,

measles, scarlet fever, diphtheria and tuberculosis, were responsible for 77 per cent of all deaths among troops quartered in the U. S. Pneumonia alone was responsible for 61½ per cent of all deaths. During the five summer months from April to August, 1918, inclusive, pneumonia was responisble for 49.3 per cent. During the autumn season, the four months from September to December, 1918, inclusive, pneumonia and influenza were responsible for 93.7 per cent. Pneumonia therefore stands out as the one infection against which the greatest efforts should be directed.

The actual number of deaths and the annual rate per 100,000 from each cause for the summer season are given in Table 2. The average strength of the troops in this country at this time was 1,420,000. This number is a fairly representative average, for at no time did the strength drop below 1,300,000, nor

TABLE 2

CAUSES OF DEATH
All Troops in the United States
Five Summer Months, Week Ending April 5, to Aug. 30, 1918
Average Strength—1,420,000

DISEASE	NUMBER OF DEATHS	ANNUAL RATE PER 100,000
Pneumonia	1679	279.
Diseases other than here mentioned*	665	111.
Meningitis	248	41.3
Tuberculosis	109	18.1
Empyema	86	14.3
Scarlet Fever	26	4.3
Typhoid and Paratyphoid fever	20	3.3
Measles	19	3.2
Diphtheria	5	.84
Total disease	2857	474.
Causes other than disease**	558	92.8
All causes	3415	567.

*Includes appendicitis, septicemia, heart disease, nephritis, etc.
**Includes burning, fracture, suicide, gunshot wounds, etc.

(See Chart III)

did it at any time exceed 1,700,000. The strength increased gradually from April through August, the maxium occurring in the week ending August 16, there being at that time 1,678,000 men on the army rolls in this country.

Taking up the summer season we see from Table 2 that next to pneumonia as a cause of death, is the group designated "diseases other than here mentioned," which includes for the most part the noncommunicable diseases, such as appendicitis, septicemia, heart disease, etc. The annual death rate per 100,000 for pneumonia was 279; that, for this miscellaneous group of many diseases, 111. Next to "causes other than disease," meningitis stands third on the list with a death rate of 41.3. This is followed by tuberculosis with a rate of 18.1, and empyema with a rate of 14.3. The last named disease was not listed separately in the fall of 1917 but increased in prominence, and as will be seen, is a factor of no little consequence. Next follows scarlet fever and trailing after this are typhoid, measles, and last of all diphtheria. We regard it as a remarkable fact that 1,420,000 men can live together in the close association necessary

in camp and cantonment without there resulting more than five deaths from diphtheria. It is a tribute to preventive medicine that this disease has been rendered so impotent.

There were but twenty deaths during this time from typhoid and paratyphoid, and these were for the most part among men new to the service who had received their inoculation after the typhoid bacillus had gained entrance to their bodies. The deaths from causes other than disease total 558, and place this third in the list with an annual rate per 100,000 of 92.8.

The deaths and rates for the autumn season are given in Table 3. The average strength for this period was 1,493,000, the maximum at any one time being for the week ending September 13, 1918, when there were listed 1,689,000 men. The lowest strength occurred in the week ending December 27, 1918, when demobilization was well under way, there being at that time 1,036,000 men. As in the summer and in the previous winter, pneumonia is the great reaper. This season marked the period of the influenza epidemic, during which 21,053 deaths are charged to pneumonia. Influenza was recorded as having caused 1,133 deaths. Although these figures are given separately in Table 3, we have combined the two in Chart III. The annual death rate per 100,000 from pneumonia was 4,300. This is nearly eight times the rate of the previous winter, which was considered at the time high. The group of diseases labeled "other than here mentioned" accounted for 512 deaths. This would mean an annual rate of 105. "Causes other than disease" were responsible for a rate of 80.2, and this stands fourth in importance when considering influenza separately from pneumonia. Typhoid, measles, scarlet fever, diphtheria, each had less than 22 deaths, there being five from diphtheria for the four months this season, which is the same number that occurred during the five months of the summer season.

TABLE 3

CAUSES OF DEATH

All Troops in the United States

Four Autumn Months, Week Ending September 6, to December 27, 1918
Average Strength—1,493,000

DISEASE	NUMBER OF DEATHS	ANNUAL RATE PER 100,000
Pneumonia	21,053	4300.
Influenza	1,133	232.
Diseases other than here mentioned*	512	105.
Meningitis	244	49.8
Tuberculosis	225	46.0
Empyema	102	20.8
Typhoid and paratyphoid fever	21	4.3
Measles	14	2.9
Scarlet fever	10	2.0
Diphtheria	5	1.0
Total disease	23,319	4770.
Causes other than disease**	393	80.2
All causes	23,712	4850.

*Includes appendicitis, septicemia, heart disease, nephritis, etc.
**Includes burning, fracture, suicide, gunshot wounds, etc.

(See Chart III)

To better appreciate the significance of the deaths from these various causes we have presented in graphic form (see Chart III) death rates for the three seasons, winter summer and autumn, placing together the rates for each disease. A casual survey of this chart indicates that as between the three seasons, pneumonia decreased 50 per cent in the summer, and then jumped enormously

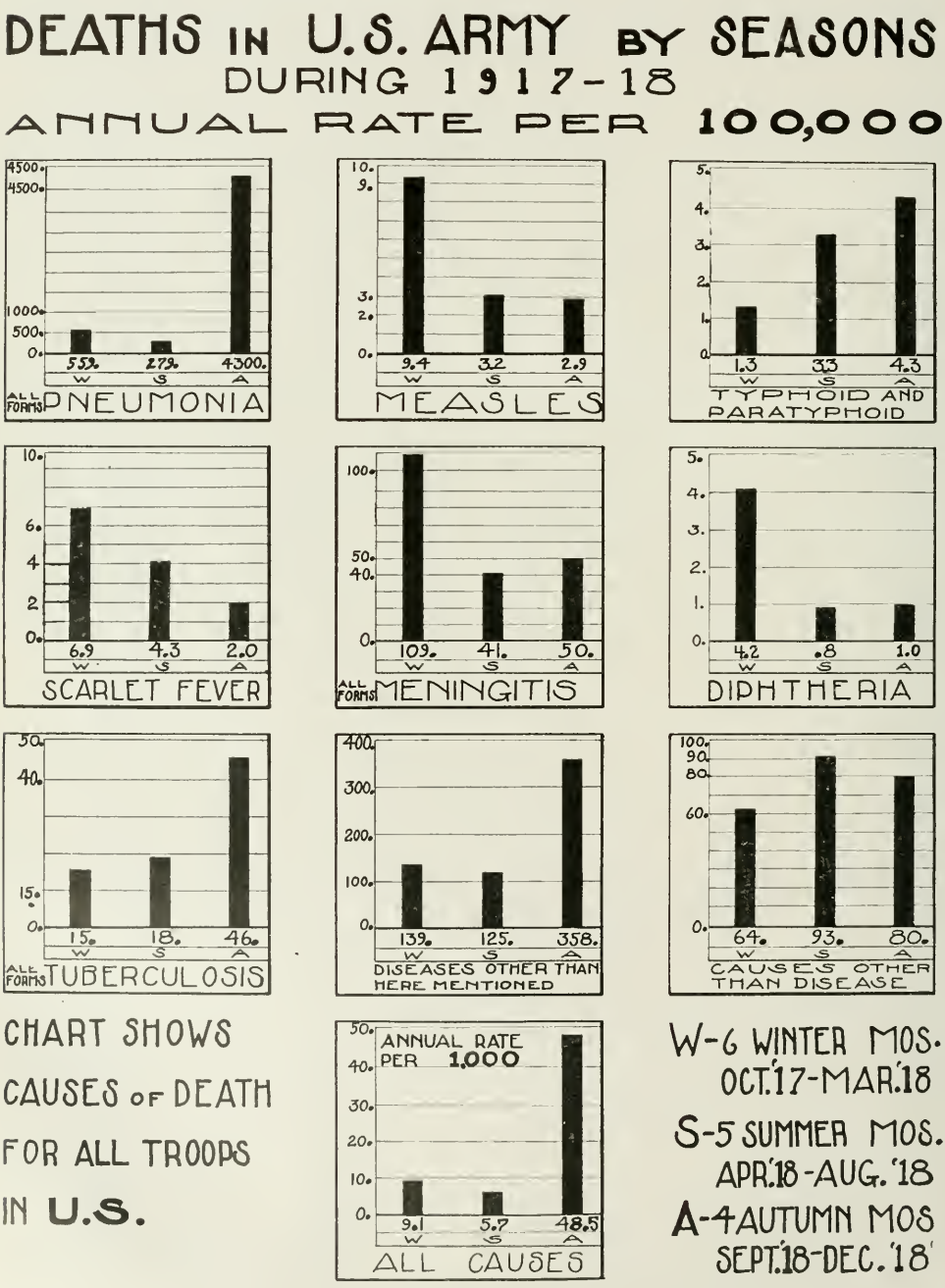


Chart III.

in the autumn. Measles in the summer time was one-third what it was the previous winter, and there was still a further drop in the autumn. The deaths from typhoid increased from winter to autumn. Scarlet fever decreased progressively. Meningitis was greatest during the winter season, a fourth this figure during the summer, and increased slightly in the autumn. Diphtheria fell off perceptibly during the summer and autumn. Tuberculosis increased slightly during the summer and perceptibly in the autumn. This increase may

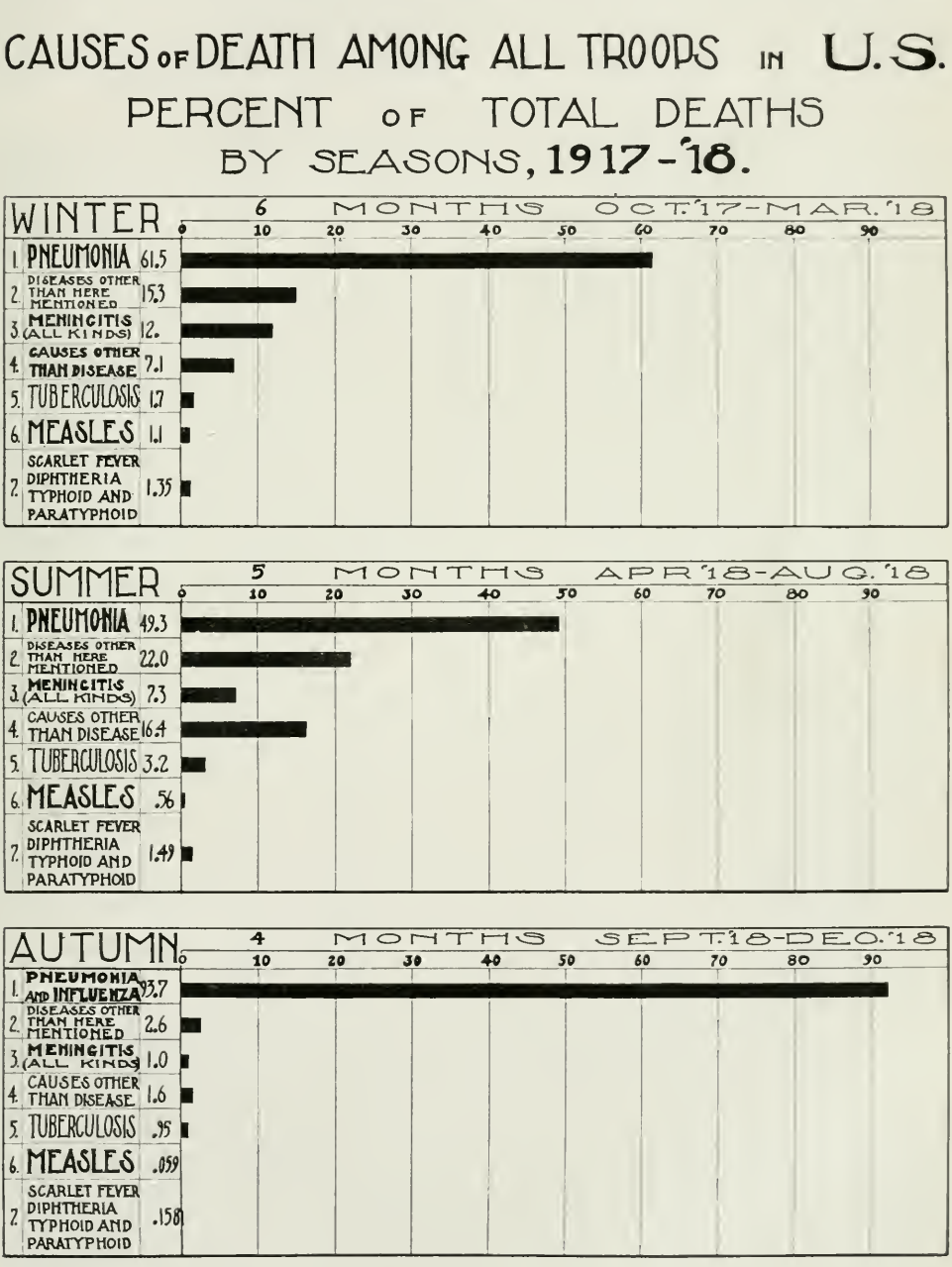


Chart IV.

be charged to some extent to the hastening of the disease by an attack of influenza. For the group of diseases which have not been treated separately, and in which we have placed influenza on the chart, there was a slight reduction during the summer and then the number increased threefold. There was not much variation in the deaths from "causes other than disease," the greatest figure occurring in the summer. The combined effect of these various causes is clear in the diagram at the bottom of the chart where there is shown the annual death rate per 1,000 from all causes for each season. The drop from 9.1 during the winter to 5.7 for the summer was offset by the enormous rise during the autumn to 48.5.

Comparison of the fatality of the disease within the seasons has been illustrated in Chart IV, the graph in this case showing the percentage of deaths from each cause. Outside the variation in the pneumonia column which is the most striking feature of this chart, we may call attention to the relative increase in the deaths from "diseases other than here mentioned" and the "causes other than disease" during the summer season. The deaths from these two causes were greater in proportion to the total deaths during the summer than during the previous winter or the autumn. The three diseases, scarlet fever, diphtheria and typhoid (and paratyphoid) make up approximately 1 per cent of all deaths.

A rate is significant only in contrast to some other rate. The army death rates may be more clearly understood if we show what has happened in civilian life. Our most accurate civilian rates are to be found by going back to the year 1910, for this was the census year, and the mortality and population statistics are more reliable than in the years following when populations have to be estimated. In Table IV we have placed side by side for the different diseases

TABLE 4

COMPARISON OF DEATH RATES OF ARMY AND CIVILIAN MALES, AGE 20 TO 29 YEARS
ANNUAL RATE PER 100,000

DISEASE	ARMY	CIVILIAN MALES
Pneumonia	*431.	45.5
Meningitis	70.6	4.6
Scarlet fever	4.7	1.9
Diphtheria	2.2	2.0
Typhoid fever	2.8	47.2
Measles	5.6	.94
Tuberculosis	24.4	206.
All causes	*760.	642.

NOTE: Army Period is average of time from October, 1917, to December, 1918, inclusive. Civilian Period is year 1910.

*The "Autumn Season" has been omitted in the Army Rates for Pneumonia and All Causes because of the influenza epidemic for which there is no counterpart in civilian life during 1910.

both the army rate and the rate for civilian males in the Registration Area. This army rate is made up from a weighted average of the winter, summer and autumn seasons. In the case of pneumonia and death from all causes, the autumn rate has been omitted. This was the influenza season and the deaths under these two headings are abnormal, and there is nothing comparable in 1910 in the civilian rates. The civilian rate is made up of males in the age group twenty

to twenty-nine years, as this is the fairest comparison with the army. These rates are expressed in terms of annual rate per 100,000.

Added significance is given to this table by expressing the rates from the two sources in terms of a ratio as is done below:

Dividing one rate by the other we see that—

Pneumonia is 9 times greater in the army.
Meningitis is 15 times greater in the army.
Scarlet fever is 2.5 times greater in the army.
Diphtheria is 1.1 times greater in the army.
Measles is 6 times greater in the army.
Deaths from all causes are 1.2 times greater in the army.
Tuberculosis is 8 times greater in civilian life.
Typhoid fever is 17 times greater in civilian lfe.

There is a wealth of significance in the relationship expressed above.

Tuberculosis and typhoid fever are the two diseases in which the army far excels civilian life. Tuberculosis is less in the army because the tuberculous individual has for the most part been prevented by the medical examination from entering the army. Typhoid fever is less in the army because every man is given a protective typhoid inoculation and because water supplies are under close supervision.

Diphtheria and scarlet fever prevail in the army in about the same degree as in civilian life.

Measles is much greater in the army because susceptible people have been drawn in from rural territory and brought in contact with the disease in camp. In other words, the exposure of susceptibles has been increased upon entering the service.

Pneumonia is greater in the army probably for two reasons: One is that the susceptible person has been placed in more frequent proximity with the individual who habitually harbors these organisms in his throat. The second is that the hardening process of camp life is a severe strain upon many constitutions, especially in the first few weeks. Cold, exposure, and fatigue are sufficient to lower the person's natural resistance to a point where either his own pneumococci become harmful or where the pneumonia-causing germs from other individuals infect him.

Meningitis has not appeared in the army as an epidemic disease. It is true that some camps have had many more cases than others, but the cases are never localized in any one organization. Rather do these spring up sporadically at widely separated points. The fact that meningitis has been fifteen times as prevalent in the army as among young civilian males is explained by the enormous multiplication of human contacts in camp. It is probable that few people are susceptible to meningitis. We know that meningococcic carriers exist. In camp the carriers rub elbows with some of this susceptible population. Meningitis occurs for the most part in the cold or changeable seasons. The greater exposure which the soldier undergoes in camp makes colds more frequent. Secretions from the sinuses pour down in greater quantity than normally, and become smeared over the hands of the soldier. As Lieut.-Col. Hans Zinsser has

so clearly stated, the common colds increase the secretion from the upper sinuses bringing down into the nasopharynx bacterial matter, which would not happen if the colds were absent. In this way it is probable that many people whose secretions are normally free from the meningococcus become dangerous carriers when the secretions from these deeper pockets are loosened. The problem facing army sanitarians is revealed in Table 4. It is pneumonia and meningitis against which the greatest efforts must be directed.

B. CAUSES OF SICKNESS

The most frequent causes of sickness serious enough to make the soldier take to his bed are those minor infections such as colds, grippe, mumps, bronchitis, etc. During the summer season there were almost 530,000 admissions for this group of diseases. Expressed in terms of annual rate per 1,000 this would be about 882. The rate for venereal disease was 156, which is about one-fifth of that of the above group of diseases. Measles stands next in frequency, and this is followed by pneumonia, malaria, and scarlet fever. Last come meningitis, dysentery, and typhoid. Admissions for disease represent 94 per cent of the total admissions. The absolute number of admissions and the rate per 1000 will be found in Table 5.

TABLE 5

CAUSES OF ADMISSION TO HOSPITAL AND QUARTERS

All Troops in United States

Five Summer Months, Week Ending April 5, 1918, to August 30, 1918
Average Strength—1,420,000

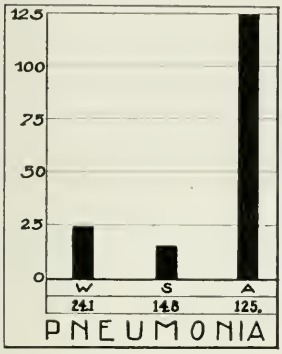
DISEASE	NUMBER OF ADMISSIONS	ANNUAL RATE PER 1000
Disease other than here mentioned*	529,887	882.
Venereal	93,959	156.
Measles	13,949	23.2
Pneumonia	8,912	14.8
Malaria	2,467	4.11
Scarlet fever	2,029	3.38
Meningitis	497	.83
Dysentery	496	.83
Typhoid and paratyphoid fever	156	.26
Total disease	652,352	1082.
Causes other than disease**	39,722	66.0
All causes	692,074	1148.

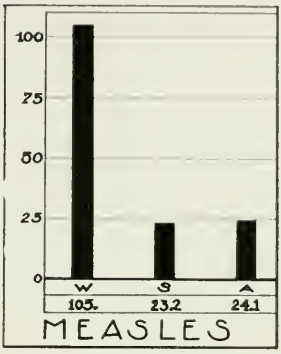
*Includes minor affections such as colds, la grippe, mumps, whooping cough, bronchitis, influenza, etc., and the rarer diseases like smallpox, anthrax, tetanus, etc.
**Includes fractures, sunstroke, gunshot wounds, etc.

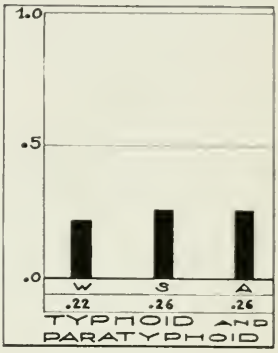
During the autumn season we find for the miscellaneous group of diseases only 381,000 admissions, which gives an annual rate of 778. This is less than the rate for the summer. However, the admissions for influenza, which were included in the miscellaneous group during the summer, amounted during the autumn to 338,000. If this were added to the miscellaneous group in the autumn, the admission rate would amount to about 1,400. The fact that the admission rate for the miscellaneous group, exclusive of influenza, was less in the

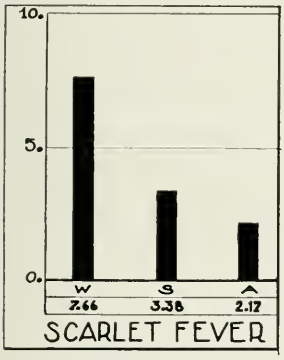
SICKNESS AMONG ALL TROOPS IN U.S. BY SEASONS. 1917-1918

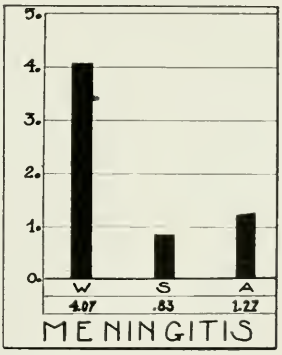
ANNUAL RATE PER 1000

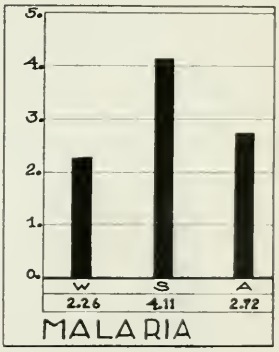


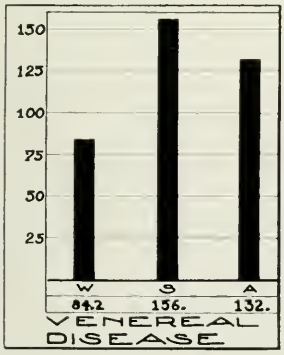


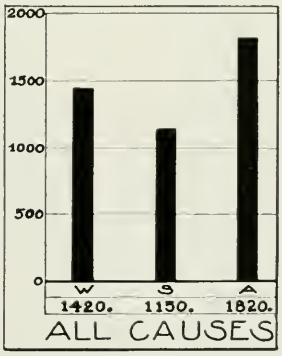












W. OCT. '17-MAR. '18

S. APR. – AUG. '18

A. SEPT.-DEC. '18

CHART SHOWS CAUSE OF ADMISSION TO HOSPITAL AND QUARTERS FOR ALL TROOPS IN THE UNITED STATES.

Chart V.

autumn indicates that many of the minor illnesses were avoided, the persons who might have had these having influenza instead. The greatest difference between autumn and summer so far as admissions are concerned, is in pneumonia. The summer rate had been 14.8. The rate in the autumn was 125. Next to pneumonia comes measles with a rate of 24.1. After this come malaria, scarlet fever and meningitis, the table concluding with dysentery and typhoid. Disease during the autumn was responsible for 95 per cent of the total admissions. These data are given in Table 6.

That we may better appreciate the significance of these admission rates we have shown in Chart V the rates for each disease by seasons, comparing one season with another. This picture is not greatly different from the chart of deaths. The pneumonia cases dropped off in the summer and increased enormously in the autumn. The greatest measles rate occurred in the winter season, dropped to about one-fifth of this figure in the summer and remained there during the autumn. Scarlet fever decreased progressively, the autumn rate being about one-third that of the previous winter. Meningitis dropped appreciably in the summer, the winter and autumn rates being about the same. Venereal dis-

TABLE 6

CAUSES OF ADMISSION TO HOSPITAL AND QUARTERS

All Troops in United States

Four Autumn Months, Week Ending September 6, 1918, to December 27, 1918
Average Strength—1,493,000

DISEASE	NUMBER OF ADMISSIONS	ANNUAL RATE PER 1000
Disease other than here mentioned*	380,928	778.
Influenza	338,342	690.
Venereal	64,672	132.
Pneumonia	61,191	125.
Measles	11,789	24.1
Malaria	1,331	2.72
Scarlet fever	1,060	2.17
Meningitis	619	1.27
Dysentery	237	.48
Typhoid and paratyphoid fever	131	.27
Total disease	850,301	1740.
Causes other than disease**	40,442	82.6
All causes	890,743	1823.

*Includes minor affections such as colds, la grippe, mumps, whooping cough, bronchitis, etc., and the rarer diseases like smallpox, anthrax, tetanus, etc. Influenza is no longer carried as a "minor affection."

**Includes fractures, sunstroke, gunshot wounds, etc.

ease was greater in the summer and dropped off slightly in the autumn. For the miscellaneous group of diseases the rate is lowest in the summer. This takes a great rise in the autumn due to influenza. At the bottom of the chart is a graph showing the rates for all causes of admission, over 90 per cent being due in each case to disease. It is surprising not to find the autumn rate much larger than it is, in view of the influenza epidemic. It is not larger because the miscellaneous group of diseases, which makes up the bulk of the admissions,

is so great normally that additional admissions for specific causes affect the total rate but slightly.

In order to understand the variation that occurs in the different seasons in the factors which send men to the hospital, we have expressed in Chart VI, the percentage of distribution of admissions by seasons. The most noticeable features in this chart are the falling off of measles, during the summer months, the increase of venereal disease during the summer months, the position of measles in the autumn, and the increase of pneumonia in the autumn. Scarlet fever, meningitis, malaria and typhoid, together caused less than 1 per cent of all hospital admissions each season.

C. CASE MORTALITY

Some idea of the seriousness of disease in the army and the variations in fatality from season to season may be gained by placing the cases and deaths from each cause side by side and computing therefrom the case mortality. This we have done in Table 7. We have grouped the records of the three seasons

TABLE 7

CASE MORTALITY RATES FOR CERTAIN DISEASES AT DIFFERENT PERIODS OF 1917 AND 1918

(All Troops in United States)

DISEASE	SEASON		CASES	DEATHS	% FATALITY
	1917		8,479	952	11.2
Pneumonia	Winter	17-18	13,393	3,100	23.1
	Summer	'18	8,912	1,679	18.8
	Autumn	'18	61,191	21,053	34.4
Scarlet Fever	1917		1,966	48	2.4
	Winter	17-18	4,253	40	0.9
	Summer	'18	2,029	26	1.3
	Autumn	'18	1,060	10	1.1
Measles	1917		44,158	20	0.05
(uncomplicated)	Winter	17-18	58,035	52	0.09
	Summer	'18	13,949	19	0.14
	Autumn	'18	11,789	14	0.12
Diphtheria	1917		1,163	12	1.03
	1917		1,027	325	31.7
Meningitis	Winter	17-18	2,264	604	26.6
(all forms)	Summer	'18	497	248	50.0
	Autumn	'18	619	244	39.5
Typhoid and	1917		238	18	7.6.
paratyphoid	Winter	17-18	124	7	5.6
	Summer	'18	156	20	12.8
	Autumn	'18	131	21	16.0
Influenza	1917		32,248	7	.02
	Autumn	'18	338,343	1,133	.34

NOTE: With the exception of the year 1917, these figures should be accepted with caution. They represent the number of cases and number of deaths within a definite period. Cases and deaths do not necessarily represent the same group of people. Some deaths may result from cases reported in a previous season. Other deaths may occur in the season following the case record and thus be omitted. For the true facts we must await the analysis of the Sick and Wounded cards.

and the figures for the year 1917 which are taken from the Surgeon General's Annual Report. A number of interesting facts are brought out in this table. In the first place we see a variation from season to season in the case mortality. During the entire year 1917 the case mortality rate for pneumonia was 11.2 per cent. During the winter months this rate increased to 23.1 per cent, more than

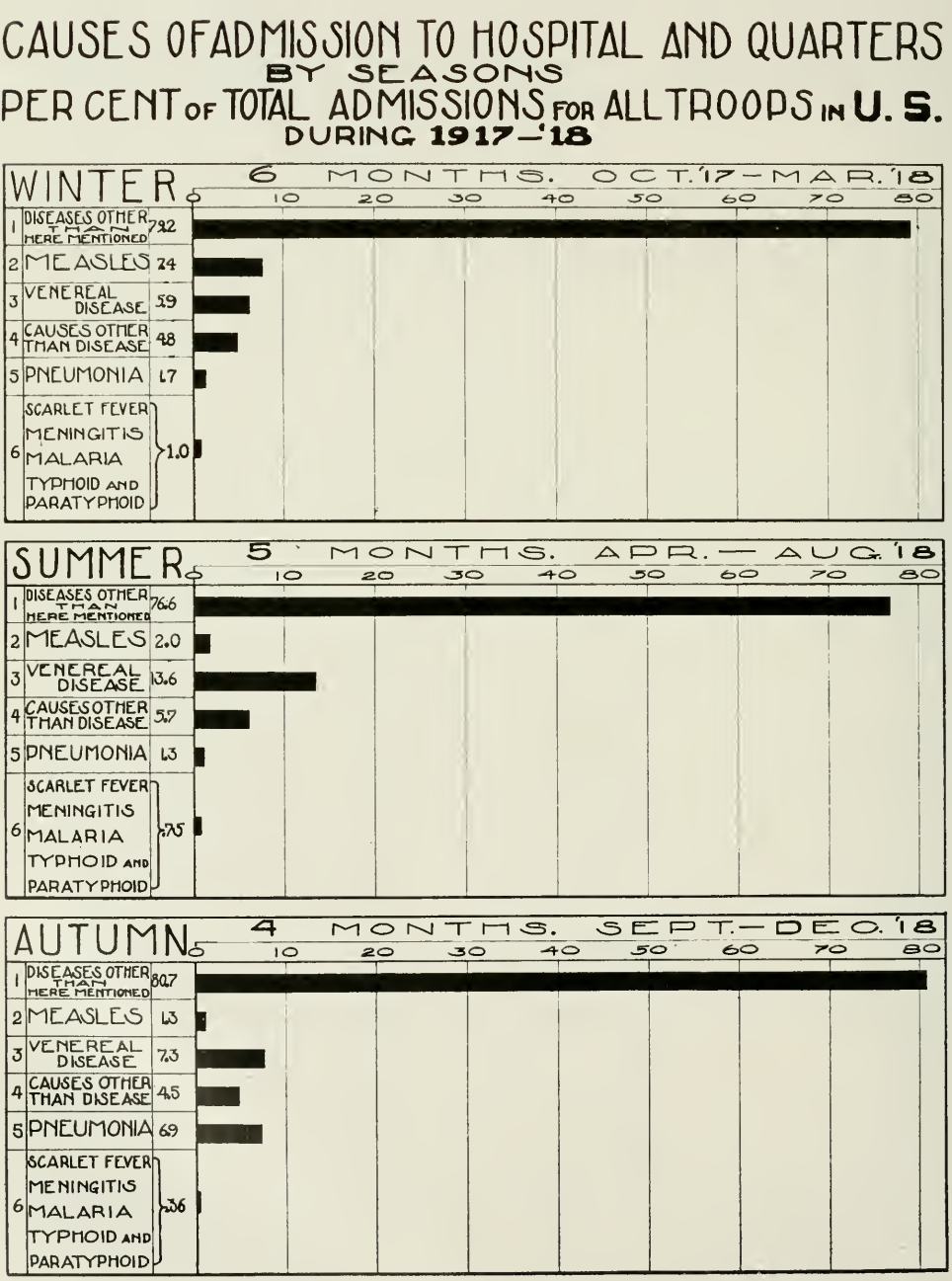


Chart VI.

double. There is an overlapping in these two seasons, three of the winter months being included in the record for the year 1917. The winter of 1917-18 was characterized by epidemics of measles and bronchopneumonia. It is these two causes, mainly the latter, which are responsible for the increased case mortality in the second period. As pneumonia decreased during the suummer, the severity of the disease likewise lessened and the case mortality dropped to 18.8 per cent. During the influenza period in the autumn of 1918, bronchopneumonia increased to a tremendous degree and not only did the absolute number of cases increase, but the case mortality rose to 34.4 per cent.

Meningitis shows a wide variation from season to season. The case mortality rate for 1917 was 31.7 per cent. During the winter of 1917-18 this dropped to 26.6 per cent. During the summer season it rose to 50 per cent. The months of April and May are included in the summer group and it is the experience in civil life that meningitis is most prevalent in the spring. In the autumn the case mortality dropped to 39½ per cent, which is higher than the rates for the first two periods.

The case mortality for typhoid and paratyphoid was 7.6 per cent during the year 1917. This dropped to 5.6 during the winter of 1917-18, then rose to 12.8 per cent in the summer and to 16 per cent in the autumn. Scarlet fever shows the highest case mortality during the year 1917. This figure dropped to nearly ⅓ this rate during the winter months and remained only slightly above this level for the remainder of the year.

The measles deaths are so few in number and so small as compared to the cases that the case mortality rates are without much significance. The only point of interest is that the rates were higher during the summer and autumn than they were during the previous winter or the previous year although the measles epidemic period is included in these latter periods. Considering the changes in the case mortality rates from season to season, we find no similarily in the different diseases. No disease had its highest rate during the winter of 1917-18. The summer of 1918 saw the highest rate in meningitis and measles. The autumn of 1918 marked high rates for pneumonia and typhoid.

D. WEEKLY INCIDENCE OF DEATHS AND DISEASE AMONG TROOPS IN THIS COUNTRY COMPARED WITH THE EXPEDITIONARY FORCE

The figures given above represent summaries for entire seasons. It is interesting to follow the disease rates from week to week. It is possible in this connection to compare rates for disease and death among the troops in this country with the rates for the American Expeditionary Force. The weekly rates expressed as an annual rate per thousand are given in Table 8.

In the first column appear deaths from all causes and these figures have been illustrated in Chart VII. The troops in this country show a higher rate than the the Expeditionary Force during November and December and up to the first week in January. From this time rates for the Expeditionary Force forge ahead and remain greater up to the second week in October. It is at this time that the influenza epidemic was at its height in this country and for two weeks the home troops unexposed to rifle fire died off at a greater rate than the men abroad who were exposed to hardship and the bullets of the enemy. Rates

for the Expeditionary Force following the third week in October are higher than that for the troops in this country and remain so for the remainder of the year.

"Death from Disease Only" is illustrated in Chart VIII. It will be noted that the troops at home had higher rates than those abroad up to the second week

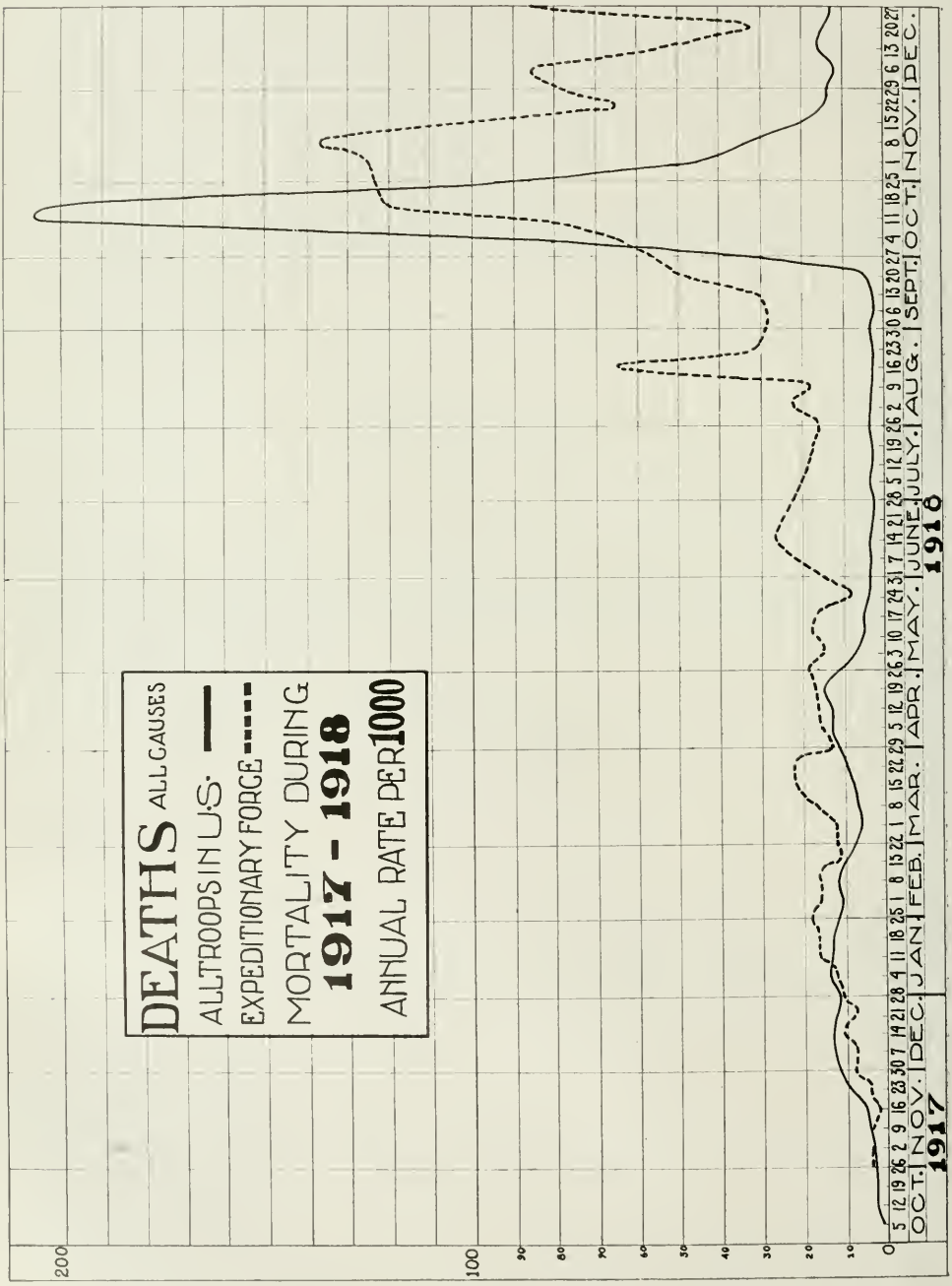


Chart VII.

in January. The leadership is then reversed for several weeks, but by the last week in March, rates for the men in this country again exceed those for the men abroad and this relationship continues with but here and there an interruption for the rest of the year. This is a striking fact and one that demands serious thought from those who are charged with the duty of recruiting armies.

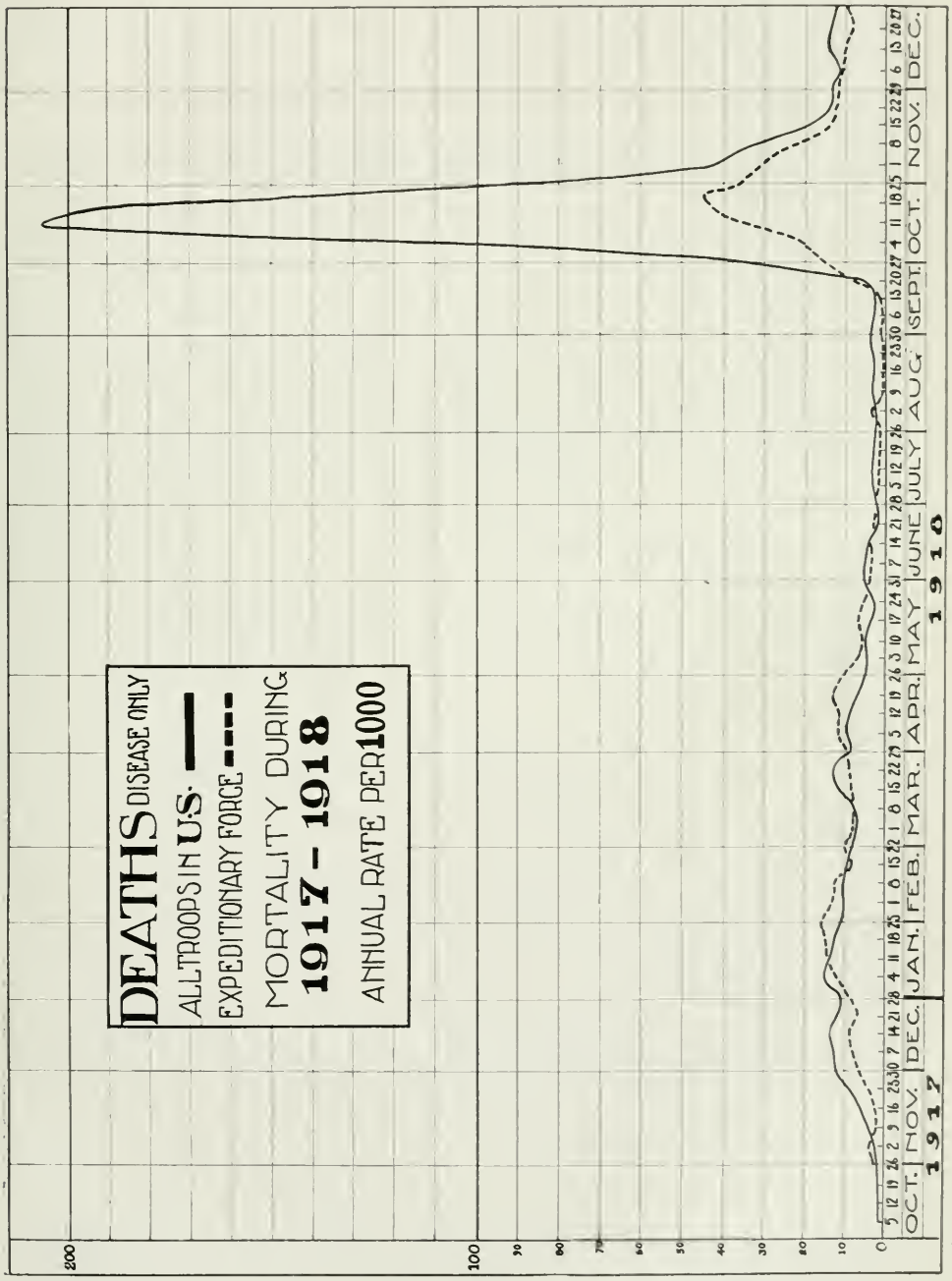


Chart VIII.

TABLE 8

DEATH AND DISEASE IN U. S. ARMY DURING THE GREAT WAR

Weekly Incidence for Troops at Home and Abroad from October, 1917, to December, 1918

Annual Rate per 1,000

WEEK ENDING	DEATHS				ADMISSIONS FOR DISEASE															
	ALL CAUSES		DISEASE ONLY		PNEUMONIA		DYSENTERY		MALARIA		VENEREAL		TYPHOID&PARA.		MEASLES		MENINGITIS		SCAR. FEV.	
	U.S.	A.E.F.	U.S.	A.E.F.	U.S.	A.E.F.	U.S.	A.E.F.	U.S.	A.E.F.	U.S.	A.E.F.	U.S.	A.E.F.	U.S.	A.E.F.	U.S.	A.E.F.	U.S.	A.E.F.
1917																				
Oct. 5	1.6	..	1.1	..	4.0	..	2.8	..	13.1	..	182.0	..	0.2	..	19.9	..	.21	..	1.5	..
12	2.0	..	1.7	..	4.8	..	3.2	..	8.3	..	118.0	..	0.4	..	24.0	..	.8	..	0.8	..
19	2.4	..	1.9	..	10.4	..	.7	..	5.2	..	114.0	..	0.6	..	26.0	..	.6	..	0.9	..
26	2.8	4.03	2.1	2.7	13.7	5.4	1.0	..	7.5	..	93.0	54.5	0.7	0.7	54.0	12.1	1.8	0.7	1.1	2.7
Nov. 2	2.9	3.7	2.1	3.7	11.8	23.7	0.5	4.3	4.8	1.2	107.0	202.	0.4	1.9	113.	8.1	1.8	0.0	2.0	1.8
9	4.8	4.1	4.1	2.0	20.4	16.7	0.8	2.1	3.6	1.0	117.0	182.	0.5	0.0	242.	27.7	2.8	0.0	1.6	1.0
16	5.9	2.7	5.1	2.2	23.1	7.2	0.3	0.0	3.0	0.9	88.0	81.1	0.9	0.0	317.	31.5	2.3	0.0	2.4	1.3
23	9.3	4.4	8.9	3.1	30.8	21.2	0.8	0.8	3.0	5.8	101.0	82.5	0.2	1.3	292.	89.2	2.9	1.7	2.7	8.4
30	12.8	8.1	12.3	6.0	22.6	14.2	0.3	0.4	2.6	0.0	101.0	75.8	0.4	0.0	176.	60.3	2.8	3.8	5.3	3.0
Dec. 7	13.3	8.3	12.6	7.0	30.9	10.7	0.1	0.0	0.9	1.5	81.0	71.0	1.1	0.3	223.0	69.0	3.8	7.9	5.1	2.7
14	13.6	11.4	13.4	8.1	31.9	25.1	0.6	1.8	1.3	1.1	63.0	122.	0.05	0.4	189.0	49.4	4.3	3.6	6.2	14.0
21	12.3	7.7	11.7	6.3	29.9	43.7	0.2	0.7	1.0	0.3	67.0	94.9	0.0	0.0	156.0	34.9	4.5	5.5	6.7	18.4
28	11.5	11.0	10.6	8.0	33.9	21.4	0.1	1.6	0.6	0.0	64.0	74.8	0.1	0.3	122.0	43.9	4.8	5.0	6.0	6.7
1918																				
Jan. 4	14.5	13.3	14.7	11.6	28.7	54.3	0.5	1.1	.7	0.6	68.0	50.0	0.04	0.0	108.0	55.8	4.4	5.2	7.4	9.0
11	13.7	16.4	13.2	13.6	38.7	52.9	0.2	1.7	1.3	0.8	81.0	57.5	0.1	0.6	109.0	77.5	4.4	2.6	8.4	27.7
18	13.5	16.4	12.9	14.2	33.0	82.2	0.4	1.1	.7	0.2	71.0	74.3	0.04	0.4	108.0	63.4	4.0	5.7	11.2	18.4
25	11.4	17.8	10.7	15.9	36.6	59.6	0.4	2.9	.9	0.0	69.0	52.6	0.1	0.7	92.0	66.3	5.3	6.7	9.3	27.5
Feb. 1	10.9	15.4	10.0	13.1	36.1	30.0	0.4	1.0	1.4	1.0	84.0	57.3	0.0	0.0	77.0	48.4	3.6	6.3	12.7	12.1
8	11.6	16.0	10.9	12.2	35.8	33.5	0.2	0.7	1.0	1.2	70.0	57.9	0.0	0.2	57.0	25.8	5.3	1.6	14.6	13.4
15	10.3	11.6	9.7	7.8	30.6	18.5	0.2	0.2	0.2	0.2	69.0	51.7	0.0	0.2	48.0	26.4	3.2	4.2	12.1	11.1
22	8.8	12.3	8.4	9.7	21.2	21.3	0.3	0.4	0.8	0.4	70.7	55.3	0.1	0.0	42.9	26.9	2.8	6.0	13.8	10.5
Mar. 1	6.7	12.4	6.6	7.0	19.7	26.0	0.2	0.2	0.5	0.0	97.1	44.2	0.2	0.4	34.7	13.7	1.5	3.0	12.0	13.4
8	7.2	19.0	6.6	6.6	18.2	36.5	0.3	1.0	0.9	0.4	100.	48.5	0.0	0.0	36.7	16.2	1.6	6.6	10.7	21.2
15	7.6	22.4	7.5	11.1	21.0	36.2	0.2	0.7	1.3	0.0	90.6	46.0	0.0	0.2	33.7	16.5	1.6	2.5	13.2	30.9
22	9.7	23.5	8.9	12.6	23.5	46.4	0.1	0.5	1.9	0.2	78.5	59.0	0.1	0.2	34.4	8.9	1.6	3.5	11.1	22.6
29	10.7	13.5	9.8	8.0	31.7	40.4	0.3	0.5	1.3	0.0	74.3	48.7	0.0	0.0	31.5	9.2	2.1	1.7	11.4	15.2
Apr. 5	12.2	16.5	11.6	9.8	26.6	35.8	0.3	1.0	2.7	0.0	129.	49.2	0.04	0.4	29.5	10.3	1.5	3.3	11.1	13.7
12	12.2	17.3	11.3	8.8	34.6	27.8	0.4	0.6	1.7	0.4	103.	47.9	0.04	0.3	28.0	4.4	1.4	2.4	12.1	15.9
19	14.3	18.1	12.9	6.4	33.8	21.3	0.1	0.0	1.9	0.7	86.9	52.8	0.0	0.1	25.7	5.2	1.8	3.4	10.8	6.7
26	10.9	19.2	10.4	4.5	26.6	28.4	0.2	0.1	2.2	1.3	78.9	40.5	0.2	0.0	21.9	6.2	1.0	2.3	8.3	9.7

TABLE 8—Continued

DEATH AND DISEASE IN U. S. ARMY DURING THE GREAT WAR

Weekly Incidence for Troops at Home and Abroad from October, 1917, to December, 1918

Annual Rate per 1,000

WEEK ENDING	DEATHS						ADMISSIONS FOR DISEASE													
	ALL CAUSES		DISEASE ONLY		PNEUMONIA		DYSENTERY		MALARIA		VENEREAL		TYPHOID&PARA.		MEASLES		MENINGITIS		SCAR.FEVER	
	U.S.	A.E.F.	U.S.	A.E.F.	U.S.	A.E.F.	U.S.	A.E.F.	U.S.	A.E.F.	U.S.	A.E.F.	U.S.	A.E.F.	U.S.	A.E.F.	U.S.	A.E.F.	U.S.	A.E.F.
May 3	7.0	15.1	6.3	4.2	16.6	23.5	0.5	0.7	2.6	1.2	146.	35.1	0.04	0.2	22.9	8.5	1.4	2.4	5.8	8.3
10	6.6	18.0	5.3	4.6	20.0	21.7	0.7	0.1	2.4	1.1	183.	32.3	0.3	0.2	21.1	9.3	1.4	2.1	8.1	6.4
17	7.1	17.3	6.3	3.3	21.8	12.8	0.6	0.3	2.9	1.0	157.	37.8	0.0	0.0	21.0	12.3	1.3	1.4	6.4	5.7
24	6.6	8.5	5.7	2.2	14.4	20.8	1.0	1.7	2.7	0.8	129.0	75.4	0.1	0.9	18.3	9.7	1.0	1.1	3.4	3.0
31	4.9	16.1	4.0	5.4	7.9	15.0	1.4	0.43	4.2	1.0	176.	38.3	0.08	0.08	19.2	8.6	0.9	2.5	3.1	7.2
June 7	4.1	22.1	3.2	4.6	8.1	10.8	0.7	0.2	4.0	0.9	175.	38.4	0.14	0.08	15.5	8.5	1.2	1.7	2.0	2.2
14	4.3	26.0	3.3	3.7	8.6	10.0	0.9	0.0	4.7	1.2	161.	47.8	0.04	0.2	21.0	6.0	.7	2.1	1.3	3.9
21	3.4	24.1	2.9	2.3	9.6	8.6	1.6	0.3	6.9	1.3	134.	33.0	0.5	0.3	20.8	4.5	.7	1.1	1.4	2.9
28	3.0	22.2	2.1	2.1	8.5	9.2	1.5	0.7	6.6	1.2	133.	29.8	0.4	0.0	23.6	6.1	.8	1.6	1.3	4.9
July 5	4.3	20.2	3.2	1.9	7.5	9.02	0.6	0.22	6.1	0.9	189.	24.5	0.3	0.3	25.8	10.7	.8	0.9	1.5	2.2
12	3.7	19.9	3.0	1.9	6.6	8.1	0.7	0.4	7.3	0.8	145.	23.5	0.4	0.2	30.2	4.1	.7	1.7	1.8	2.1
19	3.6	18.1	2.9	1.7	10.1	9.3	1.0	0.6	5.6	0.7	167.	27.2	0.4	0.2	26.5	2.1	.6	0.9	0.9	0.9
26	3.7	16.9	2.1	1.6	9.3	9.4	1.0	2.3	5.7	1.2	182.	29.8	0.7	0.9	26.4	7.8	.5	0.9	0.5	1.9
Aug. 2	3.6	22.7	2.5	2.8	9.5	5.6	0.9	2.7	4.5	0.9	162.	21.9	0.4	1.8	21.9	5.0	.4	0.8	0.3	1.0
9	4.1	18.5	3.2	0.3	8.5	6.3	0.9	2.9	5.2	0.9	218.	19.8	0.5	0.3	25.0	5.0	.3	0.7	0.4	1.3
16	3.8	66.7	2.7	0.4	10.8	6.5	0.8	2.7	6.0	0.7	232.	20.1	0.4	0.8	24.0	6.5	.2	0.8	0.5	0.9
23	3.5	33.1	3.0	0.2	11.6	8.5	1.3	3.4	5.2	1.2	200.	19.5	0.4	1.4	26.6	11.6	.2	1.1	0.3	1.3
30	4.1	44.9	3.4	0.8	14.7	11.5	1.0	7.9	5.6	0.8	171.	19.4	0.2	0.8	26.1	5.9	.5	0.6	0.4	0.0
Sept. 6	3.2	29.9	2.7	0.3	11.3	10.4	0.4	5.2	5.1	0.4	313.	21.0	0.4	0.4	20.7	5.2	.5	0.8	0.3	0.5
13	3.3	30.9	2.4	1.1	10.2	16.5	0.8	4.8	6.4	0.8	321.	22.8	0.8	0.9	21.5	9.2	.4	0.5	0.3	0.3
20	5.4	49.6	4.5	7.9	24.1	27.3	0.6	4.1	5.4	0.6	177.	26.6	0.5	0.7	22.6	9.8	.5	0.5	1.6	0.9
27	33.2	55.5	32.5	14.6	138.	37.5	0.8	5.8	5.2	0.6	106.	23.8	0.4	0.6	26.2	8.2	.5	1.7	0.6	1.2
Oct. 4	82.7	80.5	81.8	20.1	282.	71.0	0.3	4.4	2.9	0.5	124.	18.8	0.1	0.8	22.7	6.2	.9	2.1	0.6	0.8
11	207.0	80.1	206.	41.6	592.	86.8	0.4	4.0	1.7	0.6	70.3	17.0	0.2	0.2	21.1	6.1	1.5	3.5	0.9	0.6
18	191.0	122.	190.	44.7	371.	107.	0.4	3.1	1.5	0.3	81.2	19.6	0.1	0.3	28.5	6.9	3.7	5.9	0.6	7.2
25	93.2	122.	92.7	35.0	202.	67.2	0.3	5.3	1.9	0.5	83.1	16.0	0.2	0.2	24.2	8.5	3.8	3.3	1.5	0.9
Nov. 1	44.0	126.	43.2	30.8	98.9	56.7	0.7	3.8	2.1	0.4	85.9	21.6	0.1	0.5	31.4	10.3	2.0	3.3	0.9	1.2
8	34.0	139.	33.1	21.5	81.1	40.8	0.2	6.5	1.6	0.3	173.	21.0	0.1	0.6	29.4	6.2	0.9	1.6	3 3	0.8
15	20.3	111.	19.8	12.9	45.0	33.1	0.2	4.1	2.2	0.4	191.	20.5	0.2	0.3	27.7	9.1	1.0	1.6	8.4	0.7
22	14.7	66.5	13.8	12.7	36.4	38.0	0.5	4.0	1.5	0.4	156.	18.5	0.3	0.8	26.8	7.9	0.6	2.0	4.7	1.1
29	14.1	79.6	13.3	12.6	38.7	34.21	0.4	4.0	0.8	0.4	53.5	20.4	0.1	0.3	23.4	14.5	0.6	1.6	3.	0.7
Dec. 6	12.7	85.4	11.7	11.5	39.7	31.6	0.7	2.4	1.1	0.2	31.0	21.5	0.3	0.8	23.1	5.1	1.2	2.2	2.6	0.8
13	15.5	55.1	14.9	10.4	41.4	26.6	0.2	4.8	1.2	0.2	54.7	30.1	0.03	1.3	22.2	5.8	1.4	1.9	2.5	1.4
20	14.7	32.2	13.7	7.5	37.0	30.7	0.5	1.5	2.4	0.2	64.2	26.7	0.0	2.1	21.1	6.7	1.1	2.9	3.6	1.1
27	12.9	89.8	12.2	9.2	23.4	24.4	0.1	2.4	1.6	0.6	52.4	28.1	0.0	1.0	14.3	3.6	1.1	1.9	2.5	1.0

There is more disease among the home troops because their vital resistance is reduced by the transition from civilian to army life. The rates for the Expeditionary Force are low because the new recruit and the weakling do not go across to France. The weakling is weeded out before he leaves and the new recruit becomes a seasoned soldier by the time he sails. The hardships of war

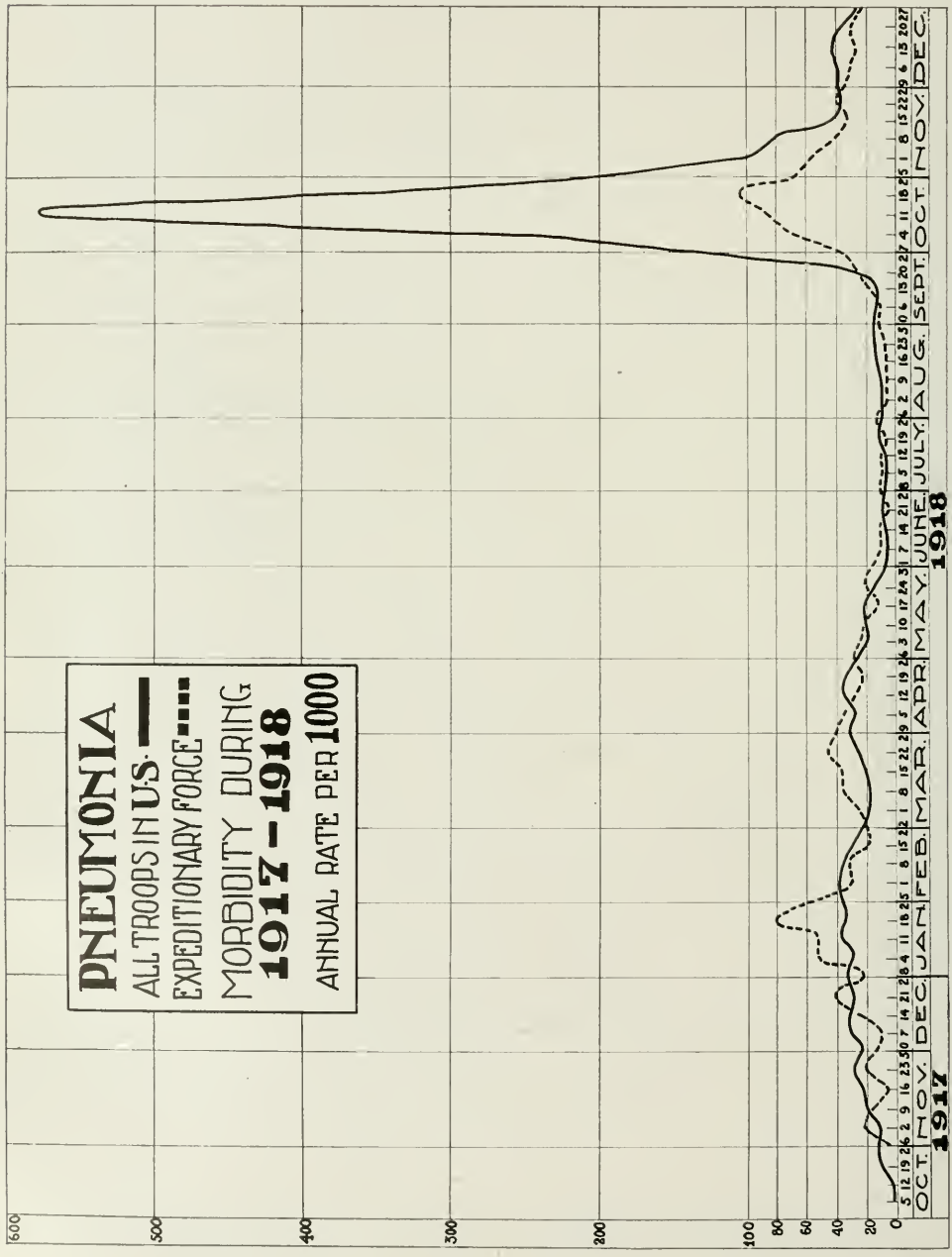


Chart IX.

and trench life, therefore, are of less consequence in making armies free from disease than is the admission of new recruits to the ranks.

Admissions for pneumonia (see Chart IX) began among the troops in this country as early as the third week in October, 1917. From that time until the last week in May the rate fluctuated from 10 to 38, remaining most of the time

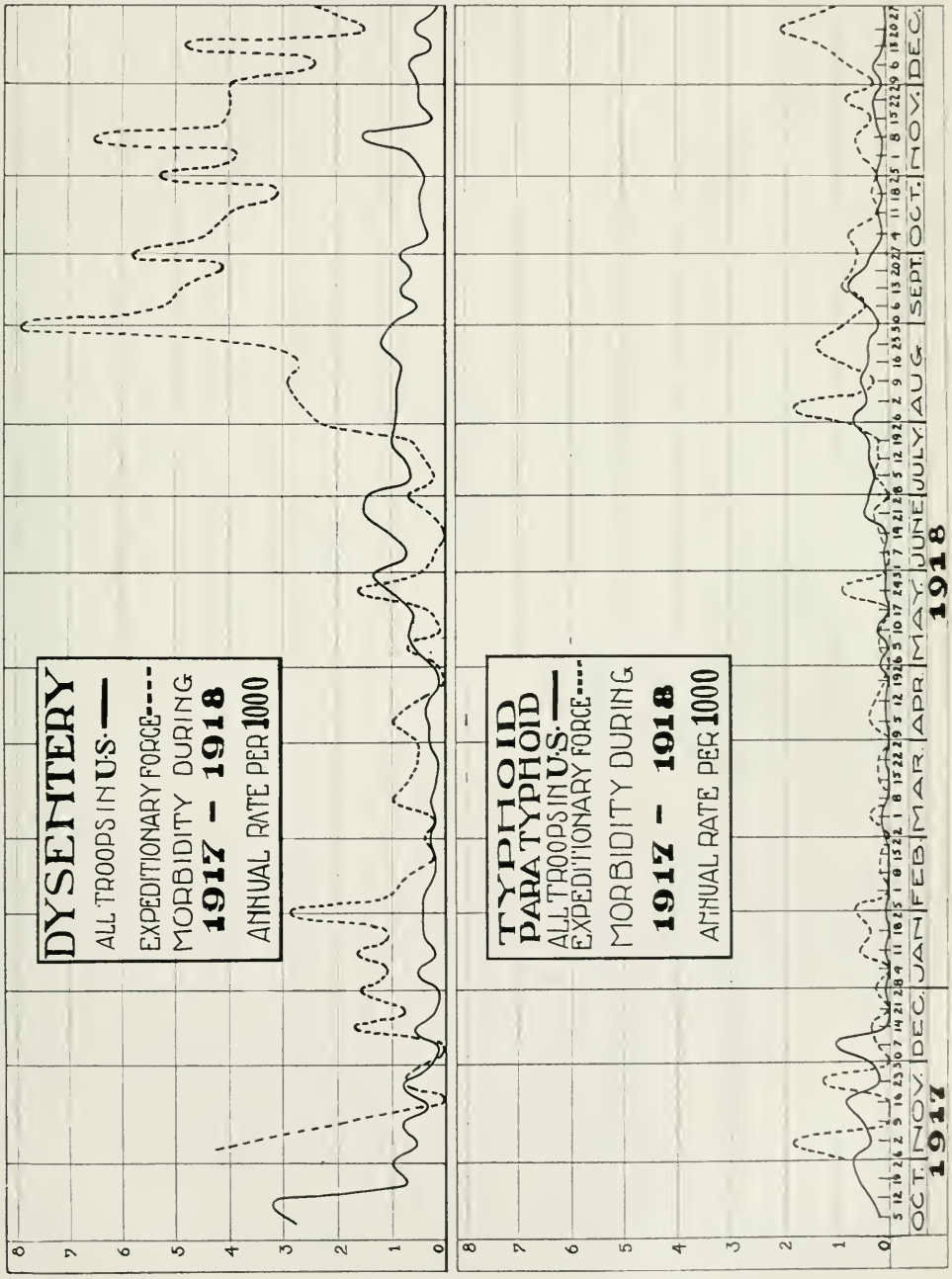


Chart X.

in the twenties and thirties. There was a dropping off after May. During June and July we see relatively little pneumonia. A slight increase occurs during the latter part of August and the figure remains fairly constant up to the third week in September when the influenza epidemic broke out. The highest rate for any week was 592 for the week ending October 11. From that time until

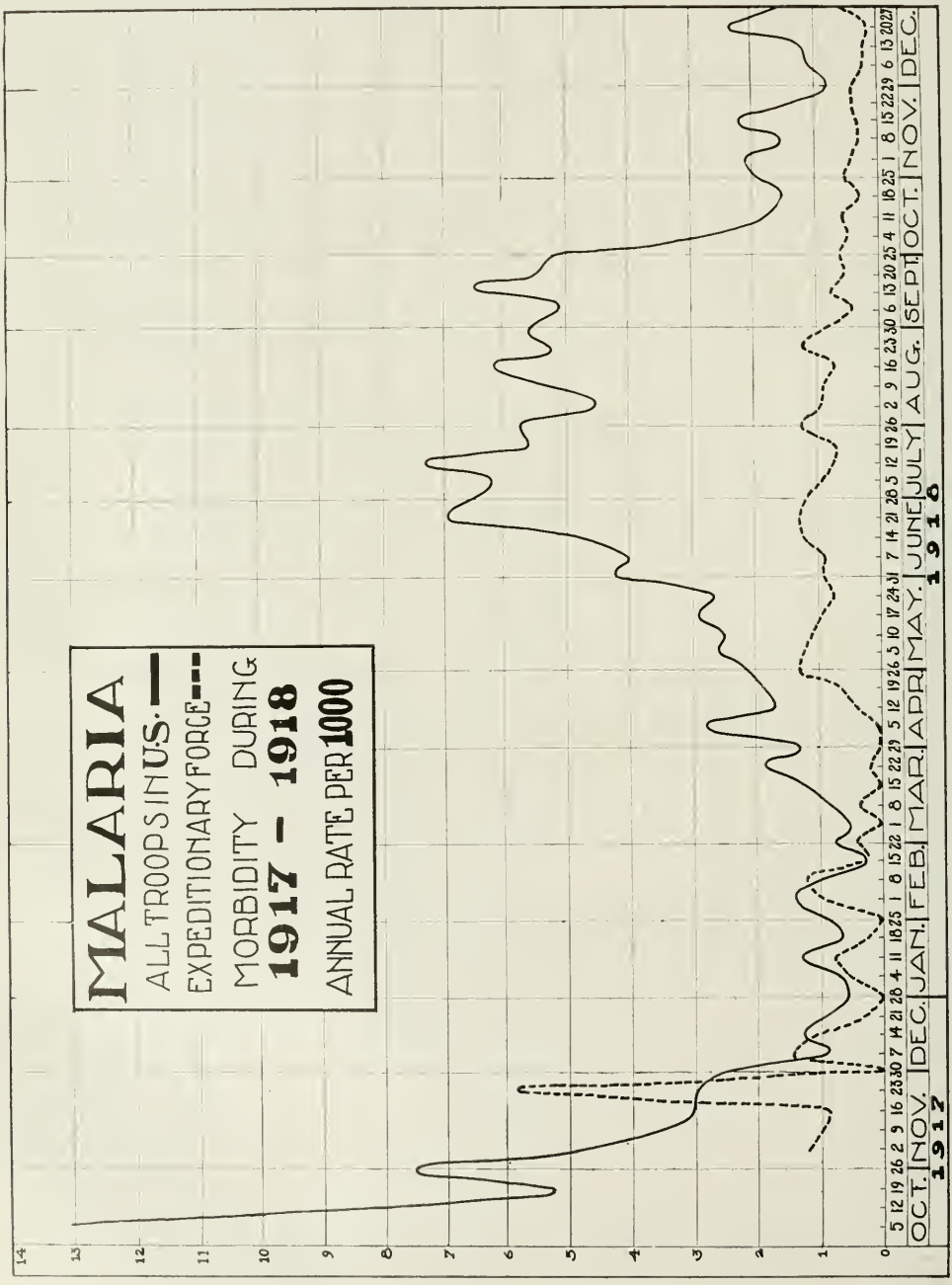


Chart XI.

the end of the year the rate does not fall below 26. Pneumonia in the Expeditionary Force is below that of the troops at home for the first three months. During January the rates for the men abroad are nearly twice as great as the troops in this country. In February the rate is less than for the troops here. From April to October the rates are similar. October and the following months witnessed much higher rates among the troops in this country.

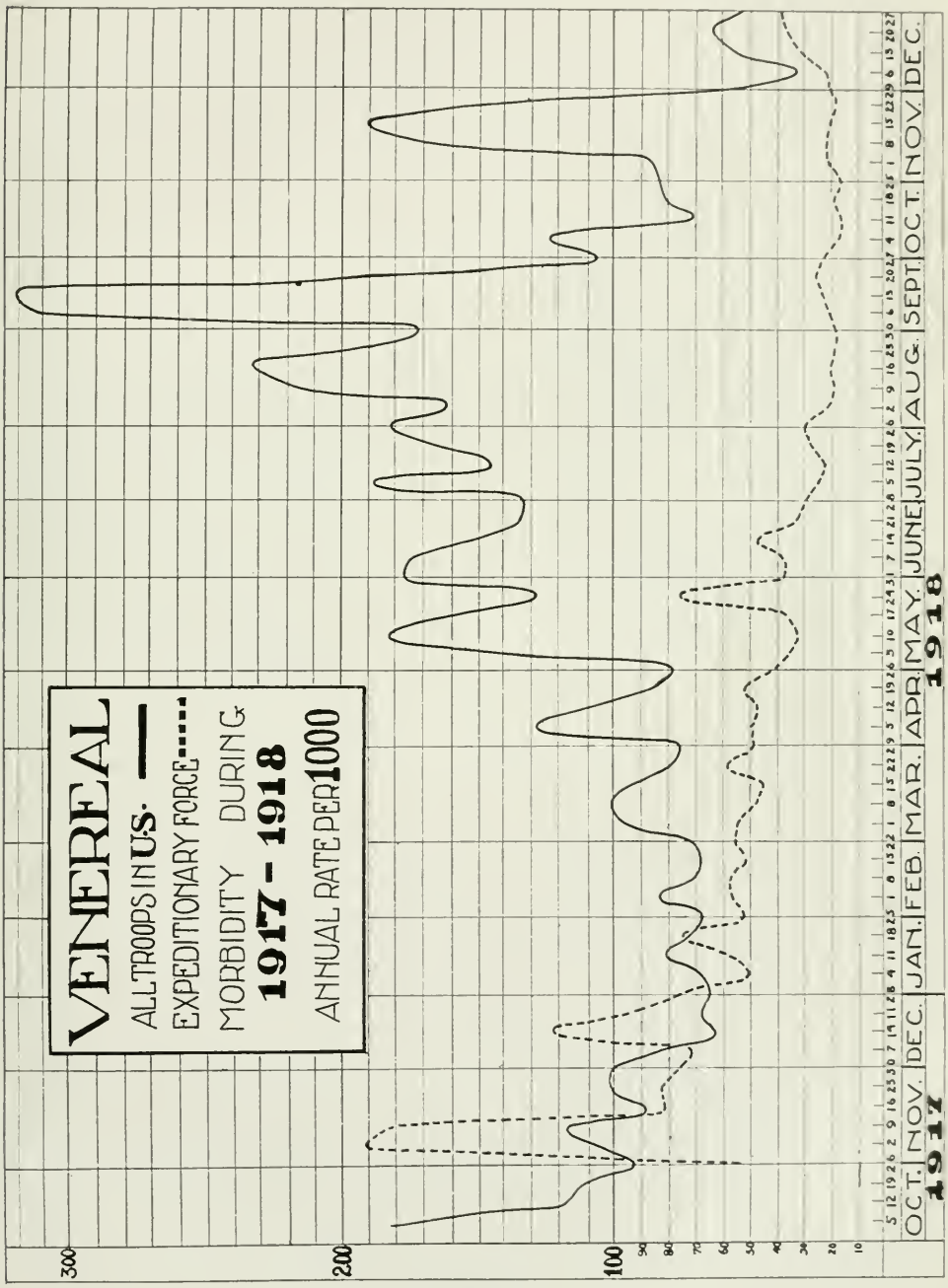


Chart XII.

Dysentery occurred to a very slight degree in this country and abroad. (See Chart X). For the better part of the time, from October, 1917, up to August, 1918, the rates in both usually were less than 1 per 1000. From August however, for the balance of the year the rate for the Expeditionary Force crept up to 2, 3, and even 7.9 for one week, the prevailing figure being around 4. During the same time in this country the rate was always below 1. Differences

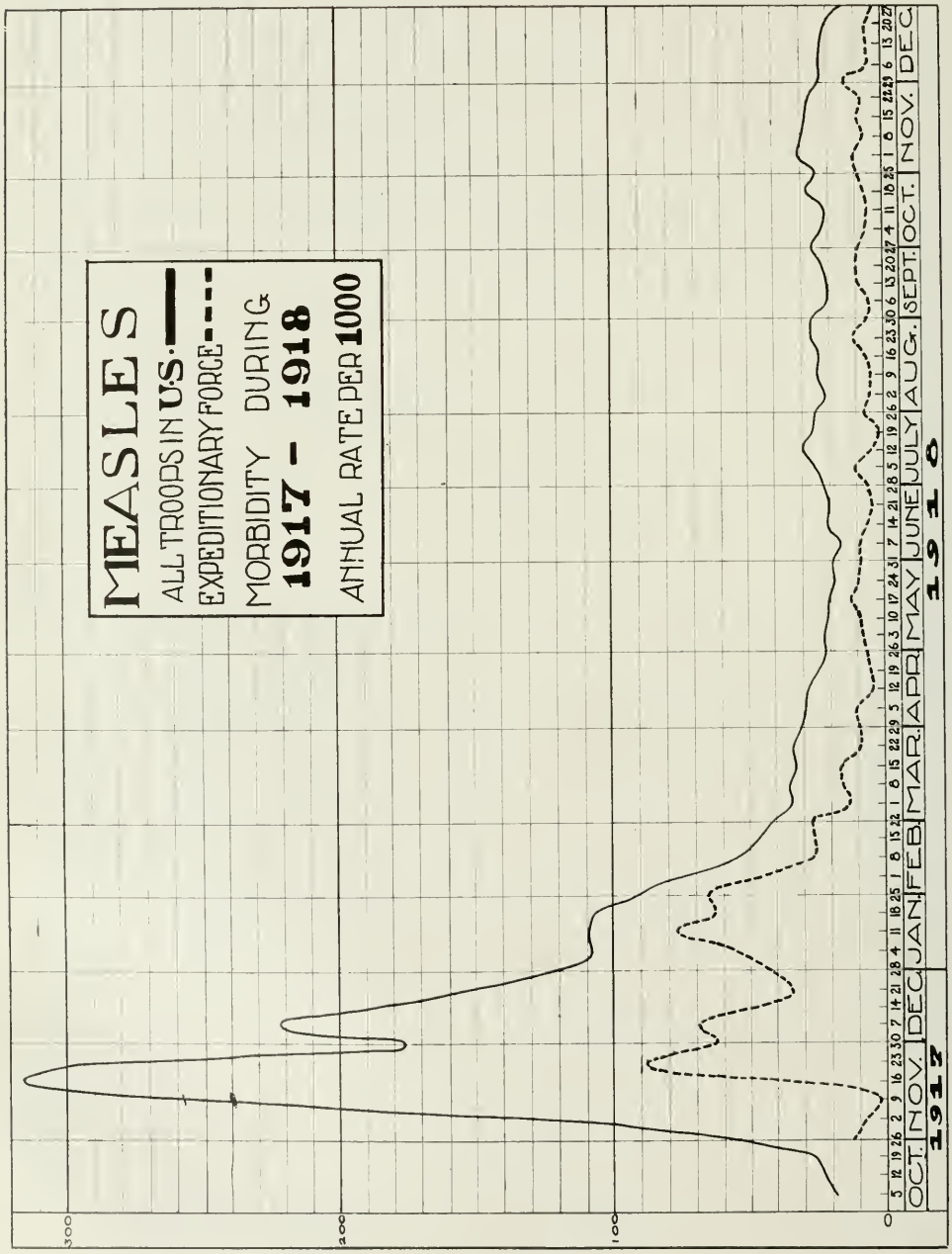


Chart XIII.

in the sanitation of the two forces are thus reflected in the dysentery incidence.

The typhoid rates were less than dysentery. (See Chart X.) On only one occasion during this entire period did the rate for the troops in this country exceed 1 per 1000, and on only seven weeks was the rate for the Expeditionary Force above 1. The highest rate for any week was 2.1, that being the third week in December, 1918. Generally speaking, the rate for the Expeditionary Force was slightly greater than for the troops in this country.

Throughout the entire fifteen months which we are discussing, malaria

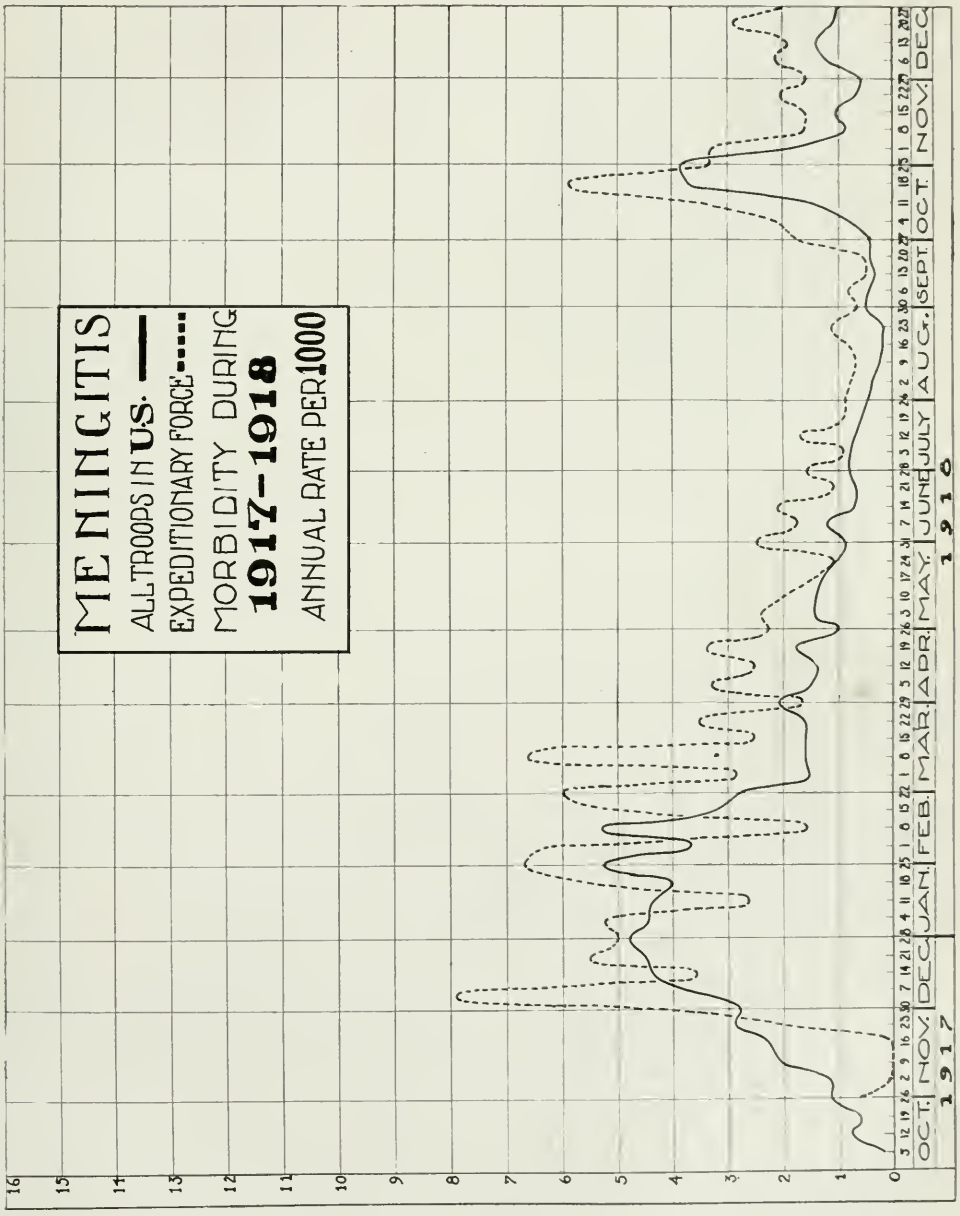


Chart XIV.

prevailed to a greater extent among troops in this country than among those abroad. (See Chart XI.) The highest rate was for the first week of this period, that ending October 5, 1917. The rate fell after November to 1 or 2 and continued until May. We are speaking of the home troops. From June till September the rate grew to 5, 6 and 7 and then returned to 1 and 2 for the re-

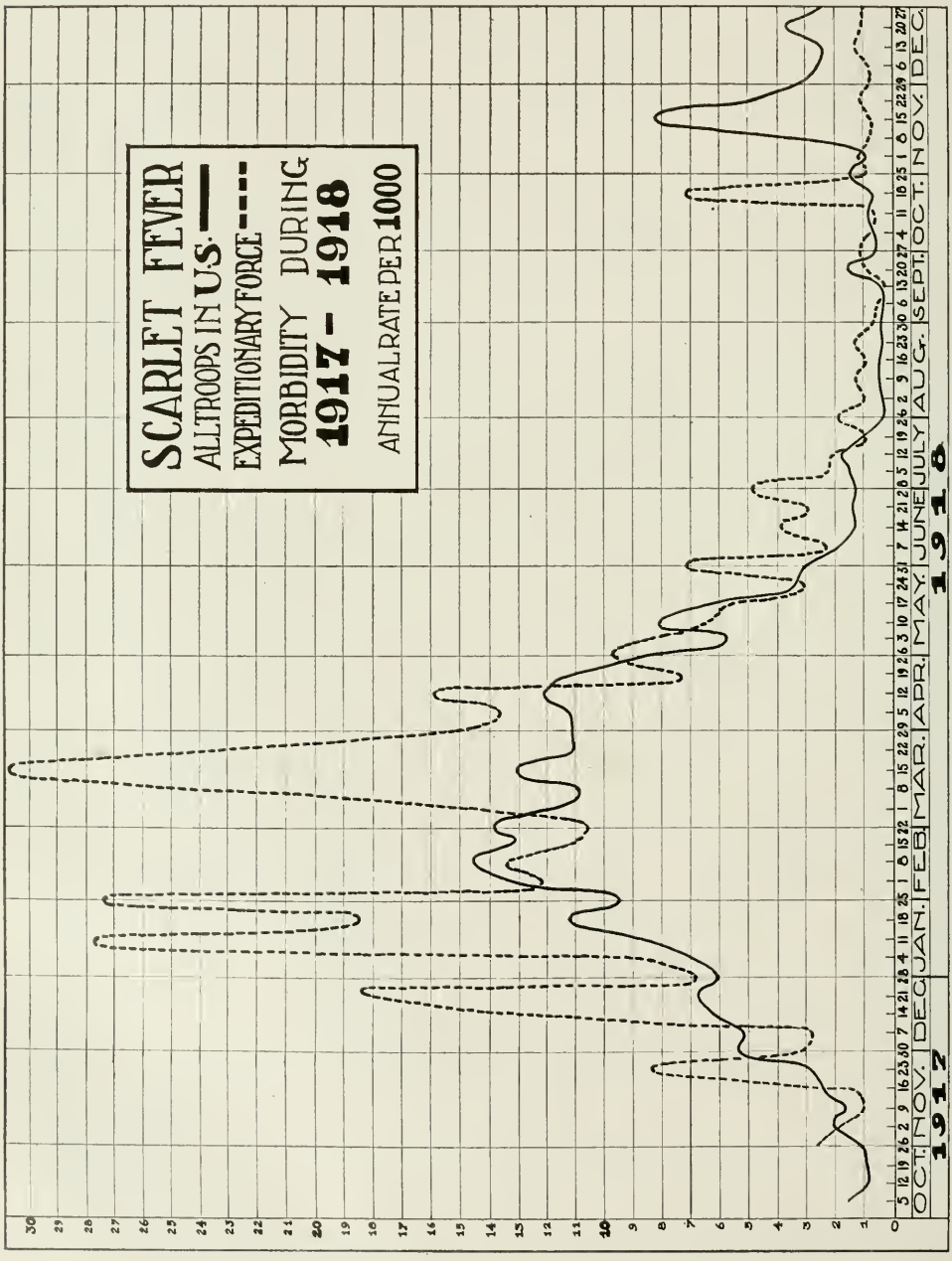


Chart XV.

maining three months of the year. For the expeditionary troops the rate was less than 1 per 1000 two-thirds of the time.

The greatest difference between the two forces will be found in the rate for venereal disease; the home troops having a rate many times that of the force abroad. This is due to the fact that a very great portion of venereal disease occurs among recruits who are infected before enlistment. In a general way the additions of new men to the army are reflected in the venereal rate. This is evident in Chart XII, where we have a high rate during the fall of 1917, the camps at that time being first established. The rate then falls until the spring when new increments are added and the rate rises. The rate continues at a high level until August and September, when new draft calls are made with a corresponding rise in the venereal rate. As the influx of new men ceases in the fall of 1918, the venereal rate drops.

The influence of the new recruit is illustrated also by the weekly rates for measles. (See Chart XIII.) Throughout the entire time the troops in this country have many times the measles admissions of the troops abroad. Apparently there was but one epidemic period, that being in the fall of 1917. From March to December the measles rate was below 40. The rate for the troops abroad was likewise higher during this early period, and after this it fluctuated between 5 and 15.

Meningitis is a disease that prevailed to a greater extent among troops abroad than among troops at home, and this relationship persisted continuously throughout the fifteen months. (See Chart XIV.) There are no great differences between the rates, but that for the Expeditionary Force is always slightly in the lead. The highest rates are from December, 1917, to March, 1918, inclusive, and in October, 1918.

Both the Expeditionary Force and the troops in this country had scarlet fever about the same time; namely, during the first four months of 1918. (See Chart XV.) The Expeditionary Force seemed to suffer more in this respect than the troops in this country, and as is the case with meningitis, the relationship is fairly constant throughout the period, or at least until November, 1918. During November and December the rates in this country are higher than those abroad.

Summing up the experiences in the two armies, that abroad and that in this country, we see first that disease is more prevalent here. The exceptions to this are dysentery, meningitis and scarlet fever. There is more disease in this country because the men are more susceptible. The home army is more susceptible because it contains a greater proportion of new men. The new, unseasoned recruit is therefore responsible for more sickness than is caused among seasoned men by undergoing the hardships of physical and mental fatigue and exposure of combat. In other words, the natural susceptibility of the individual is a greater factor in the causation of disease than environment.

A PHYSIOLOGIC INVESTIGATION INTO THE DYNAMIC ACTION OF THE HEART IN FUNCTIONAL CARDIAC DISORDERS*

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PROBABLY one of the most remarkable facts connected with cases of functional cardiac disease, as encountered in military service, is that no definite abnormality of the cardiovascular apparatus can be found to account for the "effort syndrome." The results of physical examination are either entirely negative or at most bring out a systolic murmur of doubtful import or a slight increase in the area of dullness. Modern instrumental means have also not contributed anything to elucidate the condition; graphic methods have shown nothing of importance; blood pressure studies have yielded only uncontrollable data upon which to build fanciful hypotheses. The electrocardiographic studies so far undertaken indicate that the impulse spreads in a normal manner and rate across the conducting system of the heart—this, it may be added, we are able to confirm.

Nevertheless, the impression can not be eradicated that, when a patient presents such ostensible symptoms—at times amounting to extreme distress—as are designated by the term "effort syndrome," some distinct and tangible abnormality of the cardiovascular apparatus must exist. On *a priori* grounds, one naturally suspects the contractile function of the ventricular myocardium. How do the cardiodynamics of normal individuals and of those with functional disorders compare? This is a question that merits every investigation that modern methods and apparatus can suggest. As a prelude toward such a study, we determined to investigate the duration of the isometric period and the length of systole in those cases upon the basis of considerations which must be briefly presented.

For a number of years, Frank, Tigerstedt, Piper, Starling and the writer[1] have been engaged in studying the dynamics of the ventricle by means of optical manometers recording with a high degree of precision. Such studies have shown that when the ventricles begin to contract, the pressure within the cavities is immediately elevated. This quickly completes the closure of the a-v valves already begun toward the end of auricular systole (Henderson and Johnson)[2] (Dean).[3] As the semilunar valves remain closed while the pressure continues to rise for another .03 to .04 second, the ventricle contracts isometrically, i. e., the ventricular musculature is unable to shorten because no blood is expelled from the cavities and therefore all the energy developed is expended in raising the intraventricular pressure. To this period of rising tension, one of us has given the name "isometric period." Upon opening of the semilunar valves, blood is

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From the Cardiovascular Service U. S. Army, General Hospital No. 9, Lakewood, New Jersey.

ejected and the ventricular fibers shorten. This is the "ejection period" or the "auxotonic period" of the heart.

Experimental evidence has shown in a fairly satisfactory manner that whenever the contractile power of the ventricles is impaired, the pressure rises less rapidly within the cavities during the isometric period and, consequently, this period is lengthened. This being so, the period of systole is lengthened. It is therefore evident from such experimental work that the impaired ventricle differs from the normal in having a longer isometric period and consequently an increased duration of systole.

A similar, but more general conception has been suggested by Lombard and Cope,[4] who, impressed by the fact that the period of contraction is lengthened in fatigued skeletal muscle, conceive it possible that the fatigued cardiac muscle may similarly show a prolonged systole. According to this view, the systole in the functionally impaired heart would not be terminated as early as that of the normal heart, such systole being longer without any necessary lengthening of the isometric period.

Is either one of these deviations perhaps present in the case of functional cardiac disorders? To throw light on this question, we compared the duration of the isometric periods and the entire systolic period of functional cardiac cases with those of normal subjects and with organic heart cases.

METHODS OF STUDY

An accurate study of the isometric period and duration of systole requires a most reliable means for their determination in man. Frank has pointed out that the isometric period is not a presphygmic event as has long been taught, but is marked as a small preliminary wave on the carotid pulse curve, when accurately recorded by optical capsules. In clear-cut records the duration of this period may therefore be directly determined. The end of systole is also clearly indicated by a sharp incisura so that the entire interval of systole may thus be directly calculated.[5] It was soon found, however, in routine examination of patients that many tracings were obtained in which the beginning of the preliminary wave was in doubt, especially when, as sometimes happened, a double vibration preceded the primary rise of pressure. It was therefore necessary to record simultaneously the heart sounds which was conveniently done by the improved sound recording capsules described by one of us and Dean.[6]

Technical.—In order to determine with precision the onset of the isometric period, a little construction is necessary, as the following considerations will show:

The main vibrations of the first sound coincide with the beginning of the ventricular pressure rise and therefore mark the onset of the isometric period. The vibrations of the second sound fall a short interval after the end of systole and correspond with the bottom of the incisura of the pressure curve in the aorta. To correct accurately for delay in transmission of vibrations to the neck, it is necessary therefore to place a pair of dividers with one point on the onset of the first sound vibrations and the other on the second sound vibrations and transfer the set dividers to the carotid curve so that one point is placed at the bottom of the incisura. The other point then cuts the wave representing the beginning of the isometric period. The interval between this mark and the rise of the primary wave gives the isometric period, while the distance from this mark to the beginning of the incisura gives the duration of the total systole. It is obvious that the correct interval for systole so determined is slightly shorter than the interval between the onset of the two heart sounds.

Relation between Duration of Systole and Cycles of Different Length.—It has been a generalization in physiologic teaching that any change in the duration of the cardiac cycle occurs at the expense of diastole, the period of systole being unaffected. Careful studies have shown that, while the major change occurs in diastole, systole is also affected. This variation is so pronounced that it actually affects the duration of systole from one heartbeat to another. This has been recently studied in great detail by Lombard and Cope[4] who found it necessary to establish an average period of systole for every length of cardiac cycle. Inasmuch as their data were published only in preliminary form and were, moreover, obtained by tambours recording on a smoked surface, therefore not taking into account the isometric period, it was necessary to first study a similar series of normal cases with which to compare the functional cases of cardiac disorder. To these classes of individuals studied was added a third of undoubted but well-compensated organic valvular disease. The cases of each group were carefully selected by Major F. Peabody and each case was placed in its group only after careful examinations and conferences between Major F. Peabody and the members of his staff. Since Lombard and Cope have recently[7] found considerable variation in systole between the standing and sitting posture, it is desirable to add that all observations were taken in the sitting position.

RESULTS

A. Normal Subjects.—Normal subjects were selected from the military service, being largely officers who had undergone careful physical examination. The results were first tabulated after the following scheme: After each subject in a column headed "cycle," the duration of the longest and shortest cycle was recorded. The figures for the duration of the isometric period were then extended in a column corresponding to the duration of systole. In this way the duration of the isometric period and of systole was conveniently tabulated for cross reference. Thus, figures for cycles ranging from 1.07 sec. to .59 sec. (corresponding to heart rates of from 56 to 100 per minute) were available. As the data in regard to heart rates above 80 per minute were rather scant and no rates above 100 per minute were encountered during rest, some of these subjects were requested to exercise by hopping one hundred times on one foot and the records were again taken as soon thereafter as possible. The data were similarly collected and tabulated. In order to economize space, these and similar tables are not now published but the combined data regarding the duration of systole were plotted in a common chart shown in Fig. 1. In this and subsequent plots, the dots represent the data obtained during rest, and the crosses, the data obtained after exercise.

Results.—The following results may be briefly emphasized:

1. Of 24 cases studied, 6 (25 per cent) had a pulse rate over 80 while resting.

2. The duration of the isometric period in man is somewhat variable and bears no definite relation either to the heart rate or the duration of systole. The extreme ranges were from .025 sec. to .08 sec. although the largest number of cases came within the range of .04 - .06 sec.

3. The general trend of the plotted curves, shows that the duration of sys-

tole becomes progressively greater as the cardiac cycle increases. *In general, it may be said that the duration of systole in normal men is below .25 sec. when the heart rate is above 100 per minute; averaging about .25 sec. when the heart ranges from 80 to 100 per minute, and about .28 to .30 sec. when the heart rate is between 66 and 80 per minute, while it is distinctly longer than .30 sec. when the heart is slower than 66 per minute.*

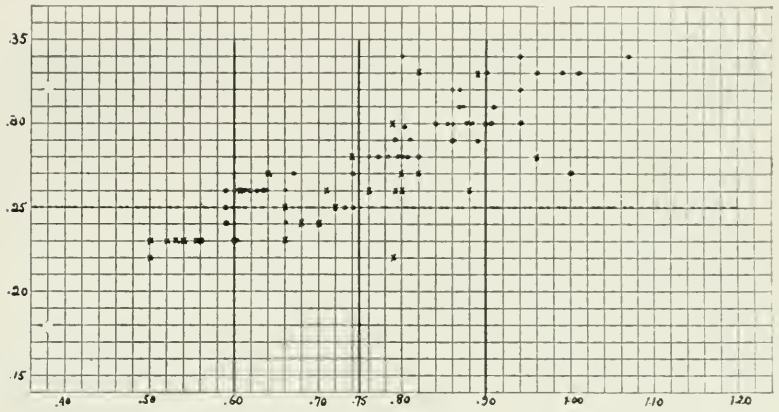

Fig. 1.

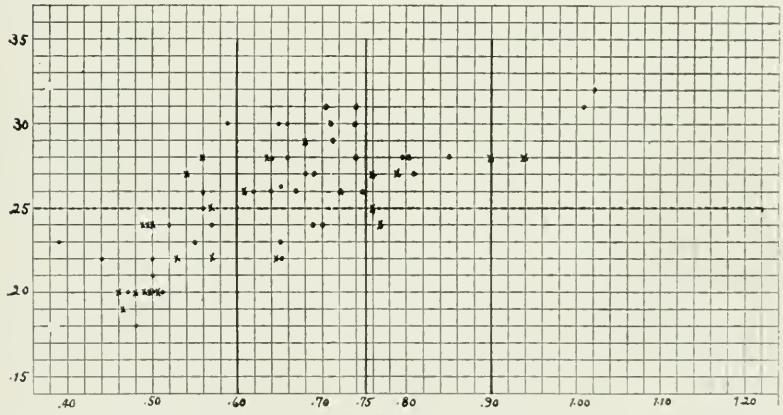

Fig. 2.

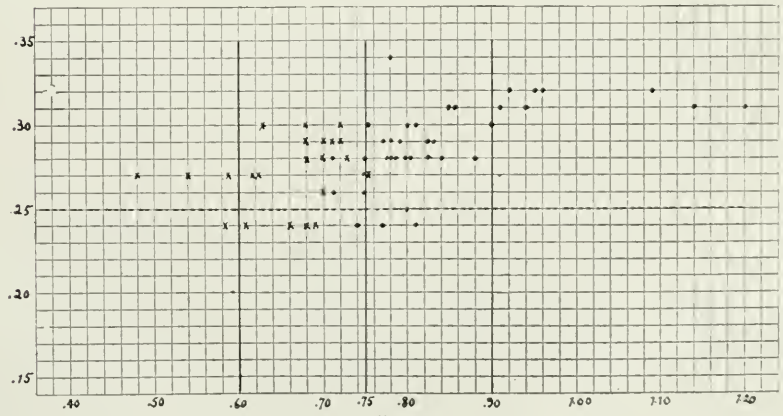

Fig. 3.

B. Functional Cardiac Cases.—The results obtained from functional cardiac cases during rest and exercise were similarly tabulated and from these the plot shown in Fig. 2 was made. The results may be briefly summarized:

1. Out of 25 cases examined, 21 (84 per cent) had a pulse rate above 80 per minute during rest. This confirms the general clinical observation that cases of functional cardiac disorders have a much more rapid heart rate than normal subjects.

2. As in normal hearts, the duration of the isometric period with few exceptions falls within the range of .04 to .06 sec. and bears no definite relation to the duration of systole. *It is clear that these hearts do not show any demonstrable deviation similar to the depressed myocardium of experimental animals in which the duration of this period is lengthened.*

3. Owing to the fact that the largest number of normal hearts have a rate below 80 per minute but can be accelerated above this rate by exercise, and by far the largest number of functional cases have rates above 80 per minute even at rest, we are justified in comparing only the data within the range of 80-100 per minute, for in this range alone are the observations sufficiently numerous and equally balanced to be really reliable. Doing this, we find that when the cycles range from .60 to .75 sec. the phases of systole are distinctly above .25 sec., the average length in normal hearts. This, it may be emphasized, is a distinct difference between normal hearts and the hearts of functional cardiac cases.

4. While the duration of systole for cycles of corresponding length, i.e., between .60 and .75 sec. is distinctly longer than in normal hearts, it is evident that the power of shortening the systolic phase is not lost. The periods plotted in Fig. 2 for cycles longer than .60 sec. indicate clearly that the duration of systole may be reduced as the heart becomes very rapid. Unfortunately not enough normal data on such high heart rate were obtainable for comparison.

C. Compensated Organic Cardiac Cases.—The organic cardiac cases studied represented a miscellaneous group of mitral and aortic lesions in which auricular action was regular and no sign of decompensation was present. These results were again tabulated and are plotted in Fig. 3. The essential features to be emphasized are:

1. Of 33 cases studied, 12 (36 per cent) had a heart rate over 80 and of these only 3 (9 per cent) had a rate over 100 per minute. This is in agreement with clinical observations that organic heart disease (uncomplicated by auricular fibrillation) is not characterized by rapid heart action.

2. The isometric period did not deviate from the normal range, showing that in compensated hearts considerable valvular derangement may exist without an alteration of the myocardial function similar to that found in experimental animals.

3. If we compare these groups of cases having before and after exercise a heart rate between 80 and 100 per minute with similar cases of normal and functional hearts, we find that there is a greater variation in the duration of systole than shown in the other groups. This is, no doubt, attributable to the varied character of the organic disorder which it was not our aim to investigate. It is evident, however, that, as in functional cardiac disorders, a large number of cases have a systolic phase definitely above .25, thereby indicating a prolongation of systole.

4. When we similarly compare the range of systole in organic cases having a normal heart rate (60 to 80 per minute) with that of normal hearts, little difference is found. In other words, we may say that hearts organically diseased when beating at the normal rate, have a systole of normal length which fails to shorten, however, as the heart accelerates.

CONCLUSION

A Possible Physiologic Conception as to the Nature of the Derangement in Functional and Organic Cardiac Disease.—A consideration of these data in the light of physiologic facts makes possible the following conception as to the cardiac derangement in cases of functional cardiac disorders and at least certain types of compensated organic lesions:

The normal heart possesses a mechanism whereby the systole is shortened when the rate is accelerated. This is especially evident when the rate increases beyond 80 per minute. In this way, we may suppose the musculature, while subjected to more frequent periods of contractile stress, is automatically spared to some extent through a shortening of systole. In functional cardiac disorders, this compensatory mechanism (whatever its nature and cause) may be entirely abrogated, or, what is more common, does not become operative until the heart has accelerated to a far greater extent (e. g., to 100 to 120 per minute). In other words, whenever the functionally disordered heart is accelerated above 80 per minute, its period of systole is not shortened as that of the normal heart and, consequently, the myocardium is exposed more frequently to a prolonged period of contractile stress. This condition, favoring the onset of rapid cardiac fatigue is more serious since the hearts of these subjects are usually rapid even at rest.

It appears that the same deficiency in the adjustment of systolic length to the duration of the cardiac cycle exists in many organic heart cases. Owing to the fact, however, that the heart rate in these individuals is usually slow, at least during rest and moderate activity, the cardiac myocardium is in this way spared from the consequences of such failure to shorten.

In conclusion, it may be stated that this report represents but a preliminary study of this question. Whether this dynamic alteration will be found characteristic of larger groups of cases, only a more prolonged study of such cases can determine. Whether the cardiac fatigue produced by such a deviation in the dynamic action of the heart is sufficient to account for the "effort syndrome" must prove the subject for an experimental investigation in the future.

We wish to thank Mr. Fred Keyes and Corporal Ford for their technical assistance in carrying on this investigation.

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NOTES ON THE EFFECT OF INTRAVENOUS DIARSENOL*

By W. C. Rappleye, M.D., Foxborough, Mass.

I. THE EFFECT ON RED CELL FRAGILITY

IT has been reported by several observers that administration of arsenic by mouth in different types of anemia has resulted in a distinct increase in the resistance of the red corpuscles to hypotonic salt solution. Gunn, in 1908, observed that the immersion of red cells for an hour in a 1:10,000 solution of arsenious acid increased the resistance of the cells to hypotonic saline and also showed later that the increased resistance conferred by arsenical substances was operative against hemolysis by hemolytic chemical substances. Hill was able to demonstrate the antihemolytic action of arsenic in chemical tests. In a case of "pernicious anemia," administration of Fowler's solution for ten days in increasing doses distinctly increased the resistance of the red cells to hemolysis by hypotonic salt solution. Before treatment, the beginning of hemolysis occurred in 0.475 per cent saline and complete hemolysis took place at 0.325 per cent, whereas the corresponding strengths of solution causing hemolysis after treatment were 0.450 and 0.275 per cent.

Similar studies have been made with the organic arsenical compounds, salvarsan and neosalvarsan. It has been found that *in vitro,* the presence of salvarsan delays hemolysis. In a very small number of clinical cases, red cell fragility has been determined before and after injection of salvarsan (0.3 gm. intravenously) and no change in the zone of hemolysis could be made out. In the treatment of a few cases of the Addison-Biermer type of hemolytic anemia, however, the resistance of the red cells to hypotonic salt solution was definitely increased by intravenous salvarsan therapy. Whether the decreased fragility is due to an increase in the resistance of the existing red cells or due to stimulation of the bone marrow and production of young red cells which, according to Snapper and others, are more resistant, is not at once apparent. The leucocytosis noted after intravenous salvarsan treatment may be some evidence in favor of the latter possibility.

During the diarsenol treatment of cases of general paresis in the hospital here, a study of the red cell fragility was made on the blood of these patients. Determinations of the zone of hemolysis were made on the blood before intravenous treatment and at intervals afterward. It must be borne in mind that the blood of these patients was essentially normal in so far as nothing of note in the cytology, hemoglobin content or blood counts was found. For this reason, one might be inclined to expect no change in the fragility determinations following the introduction of diarsenol into the blood stream.

The dose of diarsenol used in each instance was 0.5-0.6 gm. (8.0-9.0 gr.), representing 0.15-0.18 gm. (2.4-2.7 gr.) elemental arsenic, a considerable amount of arsenic were it not for the fact that it is in organic combination and 50-75 per cent of the diarsenol is promptly excreted unchanged. The further excre-

*From the Foxborough State Hospital, Foxborough, Mass.

tion of arsenic into the urine in some other form (as yet undetermined) and the rapid decrease in the amount found in the blood plasma gives but a limited opportunity for the arsenic to act upon the red cells, although it seems established that arsenic is found in the red corpuscles for some time after the plasma is free from it. The figures are given in Table I.

TABLE I

CASE	ZONE OF HEMOLYSIS BEFORE TREATMENT %	TIME AFTER TREATMENT	ZONE OF HEMOLYSIS AFTER TREATMENT %
1	0.44 to 0.31	5 min.	0.43 to 0.28
2	0.42 to 0.27	5 "	0.44 to 0.29
3	0.46 to 0.30	5 "	0.46 to 0.30
4	0.42 to 0.30	5 "	0.44 to 0.30
5	0.42 to 0.32	5 "	0.44 to 0.31
6	0.42 to 0.28	10 "	0.43 to 0.30
7	0.40 to 0.28	10 "	0.40 to 0.29
8	0.42 to 0.31	10 "	0.43 to 0.31
9	0.44 to 0.34	30 "	0.44 to 0.34
10	0.44 to 0.32	30 "	0.43 to 0.32
11	0.44 to 0.33	30 "	0.44 to 0.33
12	0.45 to 0.29	1 hour	0.46 to 0.30
13	0.46 to 0.32	1 "	0.45 to 0.33
14	0.44 to 0.33	1 "	0.44 to 0.33
15	0.46 to 0.33	1 "	0.45 to 0.33
16	0.45 to 0.28	3 hours	0.45 to 0.30
17	0.44 to 0.31	3 "	0.45 to 0.32
18	0.46 to 0.33	24 "	0.45 to 0.34
19	0.44 to 0.31	24 "	0.45 to 0.33

It seems quite evident from these figures that the fragility of normal red cells is not altered by diarsenol introduced directly into the blood stream. Such a conclusion, however, does not warrant a statement that in the abnormal blood conditions, such as the hemolytic anemias, the introduction of arsenical compounds into the blood stream does not increase the resistance of the red cells.

II. THE EFFECT ON BLOOD UREA NITROGEN

It is known that the administration of arsenic in inorganic form, as long as the substance does not interfere with digestion or absorption, increases the excretion of nitrogen, the total nitrogen of the urine being increased, especially the urea and ammonia fractions. Presumably this is caused by a mutual interaction of several factors, including capillary dilatation, a direct action on the body cells, and an action upon the gastrointestinal tract and kidneys. Weiske, however, has noted a decrease in nitrogenous excretion and especially in the amount of nitrogen in the stool and it has been maintained that the improvement in nutrition following the administration of arsenic is due to more complete utilization of nitrogen by the digestive tract and a decreased decomposition of protein by the tissues. The variations in the elimination of nitrogen, however, vary within narrow limits and possibly are not related to the action of arsenic at all. The substance disappears rapidly from the blood, being excreted or taken up by the tissues, presumably forming firm compounds with the nucleins.

Not much literature is available dealing with the effects of salvarsan or diarsenol upon metabolism. During the treatment of cases of general paresis here with intravenous diarsenol, a few observations were made upon the blood urea nitrogen values and their behavior in relation to the introduction of the organic arsenic. As commented on in the note on red cell fragility, the diarsenol given intravenously disappears rapidly from the blood stream, the greater part of it being excreted promptly. And since the balance is in organic form or probably combined with the nucleins or other body substances, the amount of arsenic available to influence metabolism must be small.

The plan followed was to draw the blood just before giving the intravenous diarsenol, i. e., secure a sample of blood from a needle already in place for the intravenous therapy, and then to secure samples at intervals after the injection, one hour, three hours, and twenty-four hours after treatment. The determinations were made by the Marshall urease method, using the aeration and titration procedure. Each determination was made on 5 c.c. of blood.

Control of the various factors influencing the blood urea values, even the fairly well-understood factors, is difficult. The influence of diet, water intake, and other features in the day's routine calls for consideration and should be controlled in order that any variations in the urea nitrogen values ascribed to the dye may be appraised with more accuracy. Accordingly, patients were given the diarsenol before breakfast, the control blood having been taken previously. On different occasions, blood was again drawn at the end of one hour, three hours, and twenty-four hours after administration, the patient having taken no food or water during the short intervals. The close approximations of the blood urea nitrogen values on the same individuals on blood drawn before breakfast at intervals of several days, when there is little or no kidney impairment, the individual remaining, of course, on a similar diet and routine, is well known. So the values obtained twenty-four hours after the diarsenol administration are relatively uninfluenced by the diet of the previous day, the blood being again drawn before breakfast.

The blood urea nitrogen values will be dependent in part on the functional efficiency of the kidneys. And the influence of diarsenol upon these values will probably vary then with the kidney function. If the diarsenol acts in any way as a renal irritant, it may be expected that the urea excretion will be accentuated in the presence of kidneys which will respond readily to the irritation. Still, our knowledge of the action of arsenical compounds upon metabolism is as yet inadequate to allow us to be sure that such action does not alter the nitrogenous substances of the blood quite independently of any renal action. The rate of phenolsulphonephthalein excretion was ascertained in most of the cases here and it can be said that, in this group of patients, the decrease or increase in blood urea nitrogen following the use of diarsenol does not seem to bear any relationship to the dye elimination. The figures are shown in Table II.

In the group of cases noted in Table II, it will be seen that the introduction of diarsenol into the blood stream affects the urea values but little, if any. The variations are within normal range. It is true that there is a slight majority of the cases which showed a drop rather than a rise in values during the first few hours after the injection. But the drop is not conclusive, surely not as striking as the

TABLE II

CASE	BLOOD UREA NITROGEN BEFORE TREATMENT	TIME AFTER TREATMENT	BLOOD UREA NITROGEN AFTER TREATMENT
1	12.9 mg. -100 c.c.	1 hour	11.8 mg.-100 c.c.
2	7.8	1 "	8.4
3	10.1	1 "	7.8
4	8.4	1 "	9.5
5	11.2	1 "	10.1
6	8.9	1 "	7.8
7	13.1	1 "	15.6
8	15.4	1 "	18.5
9	10.1	1 "	13.1
10	17.6	3 hours	16.0
11	15.4	3 "	16.5
12	9.2	3 "	8.4
13	11.7	3 "	9.2
14	14.0	3 "	13.4
15	12.3	3 "	11.7
16	13.2	24 "	11.2
17	14.0	24 "	13.7
18	8.7	24 "	10.1
19	16.0	24 "	15.4
20	9.6	24 "	11.2

drop in blood urea nitrogen noted in catatonia and reported in another connection.

III. THE EFFECT ON KIDNEY FUNCTION

The danger attending the use of salvarsan or diarsenol therapy in cases of nephritis of a nonsyphilitic character is definite. It is known that most of the diarsenol is rapidly excreted from the blood into the urine, at least when the functional efficiency of the kidneys is good. The drug remaining in the body apparently combines with the nucleins. It is not clear whether the adverse action in nephritis is due to direct action on the kidneys by the circulating drug and the attendant attempt at its excretion or is less direct. Since in such cases the excretory function of the kidneys is depressed, it may mean that only a small portion of the diarsenol is excreted as such, leaving the greater part in the body where it is gradually altered in character or combined with the cell proteins; or the portion in circulation may yield arsenical substances which compromise more completely a deficient kidney function. The relationship of kidney function and the excretion of such substances as salvarsan has been but incompletely investigated. The fact that salvarsan is a dye substance and that we judge kidney function in part by the rate of elimination of easily demonstrable dye substances such as phenolsulphonephthalein, does suggest that in depressed kidney function there is an unusual retention of diarsenol after its use, which may account for the difficulties seen in cases of nephritis in which it is used, rather than a direct action of the drug on the kidneys.

The observations made here throw no light on this feature, for the diarsenol in the urine was not followed. The point of interest was to learn whether, after the use of considerable amounts of diarsenol, there could be demonstrated evidences of renal insufficiency which could be ascribed to the drug itself. The number of cases for study was small and for that reason warrants no generalization. But it is reasonable to expect that in cases which have received many treatments

of diarsenol over a long period there should be some evidence of nephritic impairment if diarsenol itself is a kidney irritant of any severity. It is well recognized that kidney impairment is distinct in late stages of neurosyphilis and the kidney insufficiency seen in cases of general paresis which have been actively treated with salvarsan, for example, should not be ascribed to the therapy unless we can conclude that the degree or frequency of impaired excretory function is greater in treated than in untreated cases of neurosyphilis. If organic arsenical compounds are excreted without special irritation to the kidney, we can expect the renal function to be but little altered even after many injections. It seems likely, too, that the untoward effects of organic arsenical compounds in cases of nonspecific nephritis is due more to the breakdown of the compound in the body, the kidneys possibly failing to eliminate this dye as they also fail to excrete phenolsulphonephthalein, than to direct renal action. That the renal phenomena may be due to the results of the breakdown must be granted.

The rate of elimination of phenolsulphonephthalein, the blood urea nitrogen, blood pressure and urine analysis were done on a small group of cases that had received a considerable amount of diarsenol treatment. The doses had ranged from 0.3 gm. to 0.6 gm.

The figures for this group are given in Table III.

Table III

CASE	DIARSENOL	DYE %	BLOOD UREA NITROGEN	BLOOD PRESSURE	URINE SP. GR.	URINE ALB.	URINE CASTS
*G. B.	19.6 gm.	20	8.9 mg. 7.8	120-85	1.014	S. T.	Hyal. Gran.
*E. L.	24.9	10	18.5	102-70	1.009	0	Occ. Hyal.
J. M.	16.0	60	10.1 13.1	120-85	1.010-18	0	0
F. H.	29.6	60	15.6 13.1	115-70	1.024	S. P. T.	Gran.
M. J.	26.5	45	11.0 9.5	118-65 155-70	1.010	0	0
J. J.	15.6	40	15.2	124-80	1.030	0	0
R. D.	11.0	35	12.4	110-70	1.025	V. S. T.	Gran.
C. D.	32.	60	8.4 11.2	115-80	1.010	0	0
H. F.	12.5	30	15.4	152-85	1.018	S. P. T.	Gran.
M. C.	17.5	50	13.4	115-80	1.016	0	0

*In bed, showed considerable edema, general condition poor.

It will be noted that several of the above patients had received a good deal of diarsenol and so far as clinical pathology shows, their kidney function remains good. We have had a much larger group of cases under treatment and similar studies on them fail to demonstrate that diarsenol has a deleterious effect on the kidneys when their function is good at the outset.

LABORATORY METHODS

AN EDESTIN METHOD FOR THE ESTIMATION OF PEPSIN IN STOMACH CONTENTS*

By Paul R. Farrington, A.B., and Robert C. Lewis, Ph.D., with the cooperation of Philip W. Brown, A.B., Boulder, Colo.

THE purpose of the investigation here reported was to devise a practical, easy, and rapid method for the preparation of a good and uniform quality of protein, which could be substituted for the pea globulin in the method of Rose[1] for the determination of pepsin. On account of the complicated technic involved in the preparation of pea globulin and because of the difficulty of obtaining it commercially, it seemed desirable to bring this admirable method of Rose, as modified by Givens,[2] into the hands of the practitioner by using a protein which could be readily secured. No attempt was made to obtain a chemically pure protein. Our object was rather to get a product of fairly constant composition by as simple a technic as possible.

As shown in preliminary experiments, edestin has all the qualities needed in a substitute for the pea globulin of the Rose method. It is precipitated from sodium chloride solution by the addition of acid, is readily digestible at 50° C., and may be kept in dilute solution without deterioration for several months. Like pea globulin, edestin is nonpoisonous, thus removing one of the objections to the Jacoby-Solms[3] ricin method. Coupled with these essential properties we have found that edestin may be obtained by a relatively simple procedure. The following method of preparation has proved most practical in our hands.

PREPARATION OF THE EDESTIN

One hundred ten grams of finely ground† hempseed meal were shaken in a bottle with a pint of gasoline to extract a portion of the fat, and the yellow, oily gasoline was filtered off through a folded filter. The meal was then transferred to an evaporating-dish and dried by placing it in the sun, or on a radiator, first making sure that the temperature could not get above 60° C. The meal was stirred to break up all lumps and treated in a clean flask with 200 c.c. of a filtered solution of 10 per cent commercial sodium chloride (common salt). A little toluol was added, the mixture was shaken for a half-hour and allowed to stand overnight in a cool place. Next day, the flask was placed in a water-bath at 50° C. and allowed to remain there with frequent shaking until it had attained the temperature of the bath. The mixture was strained through cheesecloth to re-

*From the Henry S. Denison Research Laboratories of the University of Colorado.

†The meal may be ground in a coffee mill or meat chopper.

move the hulls, reheated to 50° C., and filtered through a folded filter in a water-jacketed funnel kept at 50° C., renewing the papers whenever the rate of filtration became too slow. The first few cubic centimeters that came through were reheated to 50° C., and, if any insoluble material was left, the extract was poured back upon the filter. It took about two hours to filter 100 to 125 c.c. from the original 200 c.c. by this method. When this amount of filtrate was obtained, it was reheated to 50° C. to make sure that no insoluble material had gone through the filter. In case a precipitate remained after heating, it was removed by filtration.

The extract was now poured into a half-gallon grape-juice bottle fitted with a two-hole stopper through which two tubes were inserted, one extending about 4 inches through the cork, and the other to the bottom of the bottle. A little toluol was added to prevent putrefaction, and the whole was mixed with 9 volumes of pure water, thus causing the protein to separate out as a white, flocculent precipitate. The short tube was closed with a piece of rubber tubing and a pinchcock, and the bottle, securely corked, was inverted, supported by a clamp and placed in a cool place. In four to eight hours the edestin settled out in the neck of the bottle, and the clear supernatant liquid was drawn off through the shorter tube, which was adjusted to remove the last portions of the clear fluid. The volume of the wet precipitate was measured, 19 volumes of water and a little toluol were added and the bottle was recorked, shaken, and inverted. The precipitate was allowed to settle and the cloudy supernatant liquid was decanted as before. The wet precipitate was placed in a large watch glass, and allowed to stand in a warm place until a dry cake of friable, brown material remained. This was ground in a mortar to a fine, almost white powder.

Four samples of edestin, prepared by the method outlined above, were found to have a surprisingly uniform edestin content. Table I shows the various steps in the preparation of these samples as well as the edestin content of the finished product. Enough edestin was obtained in each sample to carry out at least 500 analyses for peptic activity by the method proposed below.

TABLE I

SHOWING THE VARIOUS STEPS IN THE PREPARATION OF THE EDESTIN, THE PURITY OF THE PRODUCT OBTAINED, AND THE PERCENTAGE OF NaCl PRESENT

SAMPLE NO.	1	2	3	4
Extract, c.c.	123	110	112	118
Water added, 1st. dilution, c.c.	1107	990	1008	1062
Remaining, 1st. decantation, c.c.	100	85	75	93
Water added, 2nd. dilution, c.c.	1800	1615	1425	1767
Remaining, 2nd. decantation, c.c.	75	50	60	68
Edestin obtained (approximate), grams.	4.25	2.75	2.5	3.25
Edestin by Kjeldahl (5.34 × N), %	88.53	89.89	90.94	90.35
Calculated NaCl*, %	0.92	1.0	1.09	1.04

*An attempt to actually determine the chloride in a small portion of edestin (Sample 1, Table I) showed only a trace.

METHOD OF PEPSIN DETERMINATION

Inasmuch as the normal range of peptic activity is comparatively great and slight variations in the pepsin number have no clinical significance, it seemed

to us that a five tube method for the determination of the pepsin number would yield results of just as much clinical value as the finer graded seven or ten tube procedure of Givens[2] and of Rose.[1] On this account the following technic was adopted.

Solutions Required

1. Edestin solution: 0.1 gm. of the dry, finely ground edestin is weighed out on a good balance, and triturated with 10 gms. of common salt in a glass mortar, at first carefully and then more vigorously. At first, the edestin tends to collect above the salt on the sides of the mortar, but it is soon scoured off by the salt. As soon as the mixture is uniform, it is poured into a 100 c.c. volumetric flask (or 100 c.c. graduated cylinder), the last particles are brushed in and water is added to the mark. The flask is then placed in a water-bath at 50° C. and shaken frequently until all the salt and protein are in solution. A slight cloudiness, due largely to impurities in the salt, remains and is removed by filtering through a dry folded filter into a dry flask. By adding a little toluol, the solution has been kept by us for seven months without deterioration.

2. Hydrochloric Acid, 0.6 per cent: This is easily made by diluting 16.46 c.c. of normal HCl to 100 c.c. with water.

3. Diluted Gastric Contents (1:20): Five c.c. of the gastric contents to be analyzed, filtered through cotton, are pipetted into a 100 c.c. graduated flask (or 100 c.c. graduated cylinder), diluted to the mark with water, and thoroughly mixed.

Technic of Determination

Using a 1 c.c. pipette graduated in hundredths, 0.85, 0.8, 0.7, 0.5, 0.0 c.c. of water are placed, respectively, in a series of five small test tubes about 1 cm. in diameter. (Ordinary test tubes will do as well.) To each tube is then added 1 c.c. of 0.6 per cent HCl, and 1 c.c. of the 0.1 per cent edestin solution.* The edestin is promptly precipitated out by the acid as a very fine precipitate that soon becomes flocculent. To the first tube, 0.15 c.c. of diluted gastric contents (1:20) is added; to the second tube, 0.2 c.c.; to the third, 0.3 c.c.; to the fourth, 0.5 c.c.; and to the fifth, 1.0 c.c. A sixth tube containing 1 c.c. of the acid, 1 c.c. of the edestin, and 1 c.c. of diluted, *boiled* gastric juice may be added as a control. The total volume is 3 c.c. in each case. The contents are mixed by stoppering the tubes with the finger and inverting, and the tubes are then placed in a water-

TABLE II

SHOWING THE CONTENTS OF EACH TUBE AFTER THE DIGESTION IS SET UP AND ALSO THE PEPTIC NUMBER FOR EACH TUBE

TUBES	1	2	3	4	5
Water, c.c	0.85	0.8	0.7	0.5	0.0
0.6% HCl, c.c.	1.0	1.0	1.0	1.0	1.0
0.1% edestin solution, c.c.	1.0	1.0	1.0	1.0	1.0
Gastric juice, (diluted 1:20) c.c.	0.15	0.2	0.3	0.5	1.0
Peptic number	133	100	67	40	20

*We have used a protein solution of 0.1 per cent as a matter of economy, and because it permits a 1 to 20 dilution of gastric juice, gives a normal peptic number of about 100, and makes less trouble with traces of undigested protein.

bath at 50° to 52° C. for 15 minutes. Table II gives in condensed form the contents of each tube after they are ready for digestion.

At the end of the 15 minute period, the tubes are removed from the bath, the contents are mixed by inverting as before, and the tube is selected which contains the least amount of gastric juice, and in which digestion is complete a indicated by the fact that no precipitate (or only a slight trace) remains. The peptic number, which is taken as an index of the amount of pepsin present, is calculated as the greatest number of cubic centimeters of 0.1 per cent edestin solution that will be cleared up by 1 c.c. of undiluted gastric juice acting for 15 minutes at 50° to 52° C. Hence,

$$\text{Peptic number} = \frac{\text{Dilution of gastric contents} \times \text{c.c. 0.1\% edestin used}}{\text{Smallest number of c.c. of diluted contents causing complete digestion}}$$

But, as 1 c.c. of 0.1 per cent edestin is always used in each tube of the series,

$$\text{Peptic number} = \frac{\text{Dilution of gastric contents}}{\text{Smallest number of c.c. of diluted contents causing complete digestion}}$$

For example, if digestion occurs in Tubes 2, 3, 4, and 5, but not in Tube 1 (cf. Table II), the

$$\text{Peptic number} = \frac{20}{0.2} = 100.$$

In case the gastric contents have been diluted 1:20, the peptic number may be readily obtained by reference to the bottom line in Table II.

Table III

Showing Results of Determinations Made by the Proposed Method

Contents		Free HCl	Total HCl	Peptic number	
Subject	Date			Rose-Givens	Edestin Method
P. R. F.	3/25/18	68 (0.25%)	93 (0.34%)	42	100
P. R. F.	3/26/18	50 (0.2%)	71 (0.26%)	42	100
P. R. F.	3/27/18	60 (0.22%)	82 (0.30%)	42	100
F. H. F.	3/26/18	28	40	42	100
R. C. L.	3/26/18	56	65	31	67
R. C. L.	3/27/18	80	91.5	42	100
G. H.	3/27/18	21	29	18	40
R. C. L.	3/29/18	61	74		67
O. K.	3/30/18	40	56		67
X.	4/ 4/18	—	—	—	100
P. R. F.	11/25/18	—	—	—	67*

*Four determinations of the peptic number were made in this case, using each of the four samples of edestin, respectively (cf. Table I). Identical results were obtained.

The gastric analyses recorded in Table III are normal with a single exception (G. H.) and show that for contents taken one hour after an Ewald test breakfast the normal peptic number by the method proposed is 67 to 100, which happens to be a little more than twice that of the pea globulin method of Givens.[2]

SUMMARY

The method proposed for the preparation of edestin gives a product of sufficient uniformity to be used in the estimation of peptic activity without the necessity of ascertaining its exact edestin content. The procedure for determining peptic activity gives a clearer end point than that of the pea globulin method, less protein is required, and the method, even to the preparation of the edestin, is very practical for clinical use.

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TURKISH WASH CLOTHS FOR PACKS IN EXPERIMENTAL SURGERY*

By F. C. Mann, M.D., Rochester, Minn.

MANY different materials have been used for packs. Chief of these is gauze, and for general use it is doubtful whether any material can be found to replace it. In our own work in experimental surgery, however, we have found that the turkish wash cloth is more satisfactory. These wash cloths have several advantages over other materials which we have used, gauze, rubber, silk and paper. They can be secured easily, various sizes can be obtained, when placed in position they remain in place, and contrary to our preconceived idea, when moist they do not irritate delicate surfaces such as the peritoneum or pleura, nor does any of their rough surface come off into the wound. During more than a year's use they have proved very satisfactory, and they are much cheaper than the other materials.

*Division of Experimental Surgery and Pathology, Mayo Clinic.

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EDITORIALS

The Bacteriologic Examination of Suspected Typhoids

A REPORT from the Public Health Laboratories of Cairo, Egypt, contains a most valuable contribution on the above named subject. Eighteen hundred twenty-seven suspected cases were examined. The report is divided into five parts:

(1) The methods of examination.

(2) The results of the investigation, showing the relative proportion of the cases of typhoid, paratyphoid *A* and paratyphoid *B*.

(3) Conclusions as to the diagnostic value of these bacteriologic examinations.

(4) The characters of the bacilli found.

(5) General conclusions drawn from the investigation.

The methods of examination and the material studied may be divided into the following groups.

I. Blood Cultures.—The method followed in this procedure was a modification of that suggested by Conradi. The hospitals were supplied with test

tubes containing 10 c.c. of sterile ox bile. These were inoculated with from 2 to 5 c.c. of the patient's blood and then sent to the laboratory. The tubes were placed in the incubator where they remained for 48 hours. They were then shaken and a large loopful spread on an Endo-agar plate. After 24 hours in the incubator, the plate was examined. In some instances, 72 hours in the incubator measured the time, but this prolongation seemed to have no advantage.

II. Feces.—No attempt was made to render the stools fluid by the administration of drugs. The material was sent to the laboratory in corked test tubes. If not already sufficiently fluid, a thick suspension in bouillon was made and a large loopful spread on each of two plates of Endo's medium. Other preparations have been tried, but this seems to be as good as any. Both typhoid and paratyphoid bacilli grow well on it. After 24 hours of incubation, the plates were examined, and if suspicious colonies were present, subcultures were made again on Endo's medium with a further incubation of 24 hours. In this way, every culture examined was obtained from a single colony from a culture which had itself originated in a single colony. To subculture from a single colony on the original plate does not guarantee purity.

III. The Urine.—The specimens of urine examined were obtained in the ordinary way without precautions other than the thorough cleansing of the vessel used. Specimens were not centrifuged and two or three drops of each were spread on a plate of Endo's medium. Suspicious colonies appearing after incubation were purified by subculture and examined.

Suspicious colonies were purified by two subcultures before attempting identification. The same procedure was not exactly followed throughout the series. For the greater part of the time, the second subculture was introduced into a bouillon tube and a glucose-bouillon tube, the latter containing litmus and having a small Durham's tube within it to demonstrate the presence of gas. On the third day from the commencement of the examination, the glucose tube was observed, and if it had become acid the bouillon tube was tested with agglutinating sera. Occasionally the growth in the glucose tube showed plainly that the organism was not a member of the typhoid group, revealing perhaps definite turbidity without acid formation or the appearance of a pellicle, when further investigation was unnecessary, but usually the bouillon culture was tested against the three sera,—typhoid and paratyphoid *A* and *B*. Although the presence of gas in the glucose-broth tube may be taken to exclude the typhoid bacillus, its absence after twenty-four hours by no means excludes paratyphoid organisms. All organisms found to be typhoid or paratyphoid were subsequently examined in detail.

During a part of the investigation, cultures of the isolated organism on agar were prepared and tested by means of agglutinating sera. In a few instances in which negative result was obtained, but in which the growth on Endo's medium had been suspicious, the organism was again tested with a positive result. The report states that the method of identification detailed above has resulted in failure to detect any typhoid or paratyphoid bacilli which were not agglutinable by the corresponding serum, but in a routine examination it is necessary to establish a definite criterion on which to base a positive conclusion and

agglutination by the specific serum in a sufficient concentration is probably the most satisfactory that can be adopted.

Of the 1,827 cases examined, positive results were obtained in 297, or 21 per cent. This figure the investigators consider of little significance, either as an indication of the number of cases of typhoid among those presenting the clinical features, or as an expression of the value of bacteriologic examinations in diagnosis. The total number of specimens examined was 5,350, but the number from individual cases varied: from some, seven or more specimens having been received, from others only one. This variable factor may be called the degree of examination, and with this in view they have been divided into seven categories. The results are given in Table I.

TABLE I

GROUP	DEGREE OF EXAMINATION	TOTAL	POSITIVE	PER CENT
I	Six or more specimens, including a blood culture	108	35	32
II	Six or more specimens, but not including a blood culture	68	8	12
III	Four or five specimens, including a blood culture	355	76	21
IV	Four or five specimens, but not including a blood culture	88	14	16
V	Two or three specimens, including a blood culture	292	71	24
VI	Three specimens or less, not including a blood culture	483	42	8
VII	Blood culture only	433	141	32
	Total	1827	387	21

Inasmuch as the cases were examined only for diagnostic purposes, many of those which showed positive findings in the first or second specimen were not further examined. Therefore it is obvious that a certain number of cases in Group V and VII would have been in Group I or III but for this factor. The relative proportion in which the three organisms were found was as follows:

Typhoid ..... 30= 8%
Paratyphoid A .....283=73%
Paratyphoid B .....74=19%

Five cases showing double infection are not included in these figures. One case showed B. paratyphosus *A* from the blood, and B. typhosus from the feces. Two cases showed B. paratyphosus *A* from the blood and B. typhosus from the urine. Two cases showed B. paratyphosus *A* and *B* from the urine.

Beaton, director of the laboratory, speaks as follows concerning the value of bacteriologic examinations as an aid to diagnosis in suspected typhoid:

"Although the only practicable method of arriving at a diagnosis in a suspected typhoid is the agglutination reaction, under certain conditions a bacteriologic examination may be necessary. The diagnosis may be required in the first week of sickness when agglutination is not to be depended upon, or the reaction may be indefinite or fail altogether in a case in which the clinical and other conditions point positively to a typhoid infection, or the agglutination reaction may be complicated and perhaps rendered useless by recent vaccination, or the question may not be one of simple diagnosis but of the continuance of infectivity in a convalescent or the presence of bacilli in a carrier. Under any of these circumstances it becomes necessary to look for the offending bacilli in order to arrive at a definite conclusion, and if the bacillus be found this conclusion is at-

tained, but on the other hand if the bacillus be not found, no definite conclusion can be formulated. While a positive result is, other than under exceptional conditions, conclusive, a negative result is regarded as having no significance, although a negative conclusion may become more and more justifiable as the number of negative results increases. All diagnosis, clinical, bacteriologic, or otherwise, resolves itself ultimately into a question of probability. It has therefore appeared worth while to employ the considerable number of examinations involved in this investigation in an effort to throw some light on the question of the degree of probability of arriving at a positive conclusion from the bacteriologic investigation of a case of typhoid.

The number of cases in which cultures from the blood were made was 1,188, and of these 226 or 19 per cent were positive. Table II shows the time in the progress of the disease when blood cultures were made.

TABLE II

BLOOD CULTURES

	TOTAL	POSITIVE	PER CENT
All cases	1,188	226	19
First week	199	65	33
Second week	355	60	17
Third week	145	13	9
Later than third week	118	8	7
Unknown	371	80	—

These figures show that the probability of isolating the causative organism from the blood in the second week is only half that in the first week, and in the third week again only half that in the second week. However, it is seen that even in the fourth week a small percentage gave positive results.

In 206 cases shown by finding the bacilli in the blood or the urine to be actually some form of typhoid fever, the bacilli were found in the feces in only 12 per cent. If two or three specimens of feces were examined, one of which proved positive, it was only exceptionally that the other one or two proved positive too, and in the event of more than three specimens being examined, in no case did all the specimens prove positive. In 46 cases in which two or more specimens were examined and in which at least one specimen proved positive, in only eight did more than one specimen prove positive.

In 297 cases in which typhoid bacilli were found in the blood or in the feces, the same organism was found in the urine in only 6 per cent. In 51 cases in which two or more specimens of urine were examined, and in which at least one specimen proved positive, in only nine did more than one specimen prove positive.

The characters of the typhoid and paratyphoid bacilli obtained were briefly studied. In addition to the specific agglutination test, the action of each organism on carbohydrates and on milk was tested. The Bacillus typhosus should produce no change in lactose, saccharose, and dulcite, and should form acid but no gas in mannite and glucose. Of 30 strains examined, 29 gave this typical reaction, although in one case the amount of acid formed from mannite was very small. In the case of one strain, a bacillus isolated from the urine, no acid was formed from mannite after five days; this strain was agglutinated by a typhoid serum at a dilution of one in 1600.

The Bacillus typhosus consisting of 13 strains was tested on litmus milk. All produced a decided acid reaction within 24 hours and this persisted for more than a week in every case. At the end of the second week with a certain number of the strains the medium had lost its acidity, and by the end of the third week a diminution of acidity had occurred in every case; 5 strains showed reduced acidity, 6 had returned to the original color of the medium, and 2 had become definitely alkaline. No clotting occurred.

The action of Bacillus paratyphoid *A* on carbohydrates is characterized by the formation of gas and acid in dulcite, mannite, and glucose, while no change occurs in lactose and saccharose. Dr. Beaton states:

"The strains of B. paratyphosus *A* isolated proved to be very erratic in their action, and to present in this respect a striking contrast to the strains of B. typhosus and of B. paratyphoid *B*. While conforming to type in their action on lactose and saccharose (although it must be admitted that a definitely lactose-fermenting organism would have escaped recognition) they presented a considerable amount of variety in their action on dulcite, mannite, and glucose. Of 303 strains examined, 238 gave the typical reaction to some degree, although only 94 produced a sufficient quantity of acid and gas for the reaction to be considered wholly typical. The two strains giving acid only in mannite and glucose, the typical reaction of B. typhosus, were agglutinated by a paratyphoid *A* serum at a dilution of 1 in 500, and were not agglutinated by a typhoid serum."

Two hundred strains of this organism were studied as to their action on litmus milk. All produced acid after three days, without the formation of a clot, and all remained acid after thirty days, still without clotting. This constitutes the typical reaction.

The characteristic action of Bacillus paratyphoid *B* on carbohydrates consists in the absence of change in lactose and saccharose and the formation of acid and gas in dulcite, mannite, and glucose. Of 78 strains examined, all gave the typical reaction. In two, the quantity of gas formed from dulcite and glucose was small.

Twenty-four strains of Bacillus paratyphosus *B* were examined as to their action on litmus milk. All produced acid during the first 24 hours, and this reaction persisted on the second day. On the third day, more than half the strains showed a definite alkalinity, and at the end of the first week, with 20 strains, the medium was definitely alkaline. After three weeks all strains showed a strongly alkaline reaction.

The most important conclusion to be drawn from the data is the relative proportion of cases of typhoid and paratyphoid *A* and *B* found among typhoids acquired in Egypt and those acquired on the Gallipoli Peninsula. Among those from the Peninsula, 82 per cent showed paratyphoid *A*, and 18 per cent paratyphoid *B*. There were among these no typhoids. Among 40 cases known to have originated in Egypt, 5 per cent were typhoid; 87.5 per cent, paratyphoid *A;* and 7.5 per cent, paratyphoid *B*. In many of the cases it was uncertain where the disease originated. The figures show at any rate a great preponderance of paratyphoids in both groups. No definite information is available as to the amount of paratyphoid fever in Egypt before the war, but it may be said that paratyphoid *B* occurred, although to a much smaller extent than typhoid; while

cases of paratyphoid *A*, although probably occurring occasionally, were very rare. These conclusions are drawn entirely from the results of agglutination tests, and it may be assumed for all practical purposes that paratyphoid *A* was not endemic in Egypt.

It is too early to determine whether paratyphoid *A* will be established as one of the endemic diseases of Egypt, but this should in due course constitute an interesting point in connection with our knowledge of the factors determining the existence of endemic diseases, and a curve based on the relative proportion of cases of typhoid and paratyphoid *A* and paratyphoid *B* occuring in Egypt during the next few years should throw some light on the question of how far the absence of this disease from a geographical area may be due to the fact that it has never been adequately introduced into the area, and how far to the lack of conditions suitable for its development.

This report is most interesting, and at the same time, highly suggestive. It will be observed that by all the tests combined only 21 per cent proved to be one of the known forms of typhoid fever. It would be highly interesting to know what the final decision was in the remaining cases. If there be three typhoid fevers, etiologically considered, why should there not be more? If there be organisms which we now designate as paratyphosus *A* and *B*, there may be varieties which we will later designate as *C* and *D*, and so on. It is possible and indeed highly probable that so far as vaccination has failed it is due to the disease being caused by other members of the typhoid group, which in all probability is much larger than we now appreciate.

A second most interesting point brought out in this valuable report is that of the introduction of a disease into a country where it has not hitherto prevailed, and the possibility of the newly introduced organism supplanting kindred organisms already native to the country. There are many reasons for believing that in the various camps in this country different organisms became predominant and the dominating organism changed from time to time with new importations. It is possible that the great differences in the death rates in the various camps in this country may have been due to this or some similar cause.

—*V. C. V.*

The Scientific Research Fund for Study of Venereal Diseases

THE United States Interdepartment Social Hygiene Board, through its executive Secretary, T. A. Storey, Washington, D. C., announces appropriations from its Scientific Research Fund to the following institutions for the purpose of investigating "more effective medical measures in the prevention and treatment of venereal diseases:"

University of Nebraska College of Medicine

1. (a) "Investigation relative to the development of an internal urinary antiseptic."

(b) "Investigation of the value of certain anilin dyes in the treatment of gonorrhea." Both under the direction of E. G. Davis, M.D., Director of Pathological Laboratory.

St. Louis University College of Medicine

2. "Studies in infection by gonococci." Under the direction of R. A. Kinsella, M.D., Director of Department of Experimental Medicine.

Woman's Medical College of Pennsylvania

3. "A serological study of syphilis in pregnant women and new-born children with special reference to the efficacy of the accepted methods of syphilitic treatment." Under the direction of Berta M. Meine, M.D., Director of Research Department.

Washington University School of Medicine

4. "The laboratory (biological) investigation of the latent syphilitic as a 'carrier.'" Under the direction of Martin F. Engman, M.D., Professor of Dermatology.

Cornell University Medical College

5. "Serological study of the gonococcus group." Under the direction of John C. Torrey, Ph.D., Professor of Hygiene.

Jefferson Medical College of Philadelphia

6. "A series of studies for the recognition and diagnosis of treponema pallidum in venereal diseases, and the effect of various drugs and materials as germicidal agents against treponema pallidum." Under the direction of Randle C. Rosenberger, M.D., Professor of Hygiene and Bacteriology.

Yale University Medical School

7. (a) "Effect of anilin dyes, particularly Gentian Violet on the gonococcus with reference to the growth of the organism in media containing the dye and with reference to the effect on organisms in tissue (therapeutic effect)." Under the direction of J. M. Flint, M. D., and J. W. Churchman, M.D., Professors of Surgery.

(b) "An intensive study of methods for the isolation and identification of the gonococcus with a view to the determination of the homogeneity or heterogeneity of strains and their etiological relationships." Under the direction of George H. Smith, M.D., Assistant Professor, Department of Pathology and Bacteriology.

(c) "The demonstration of syphilitic nature of unusual lesions encountered at the post mortem table." Under the direction of M. C. Winternitz, M.D., Professor of Pathology and Bacteriology.

Union University Medical Department, Albany

8. "For studies on the nature of the Wassermann reaction." Under the direction of Thomas Ordway, M.D., Dean, and Associate Professor of Medicine.

The United States Interdepartmental Social Hygiene Board is composed of—

Carter Glass, Secretary of the Treasury,
Newton D. Baker, Secretary of War,
Josephus Daniels, Secretary of the Navy,
Lt. Col. W. F. Snow, Medical Corps, U. S. A.,
Lt. Comdr. J. R. Phelps, Medical Corps, U. S. N.,
Asst. Surg. Gen. C. C. Pierce, U. S. Public Health Service,
Thomas A. Storey, Executive Secretary.

Up to June 21, the Board had approved appropriations from its Scientific Fund for twenty researches distributed among twelve medical schools.

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ORIGINAL ARTICLES

COMMUNICABLE DISEASE IN THE UNITED STATES ARMY DURING THE SUMMER AND AUTUMN OF 1918.*

By Col. Victor C. Vaughan, M.C., U.S.A., and Capt. George T. Palmer, S.C., U.S.A., Washington, D. C.

Section III

Distribution of Deaths and Disease Among the Army Camps

EXPLANATORY NOTE: There are two sources of statistical data upon which the authors have drawn in making up the tables and discussions which follow. One of these is the weekly telegraphic report which is sent in from each camp and post to the Surgeon General. The other is the special reports prepared by camp officers, and forwarded from time to time to the Surgeon General. The latter source of information is more accurate because there has been time to check over the weekly reports and correct errors which are bound to creep in. These errors arise from the fact that diagnoses are changed and that the reports at times include records from the base hospital, at other times do not include them, and at still other times hospital records are counted twice in making up the consolidated report.

For the summer season and likewise for the autumn, except for certain diseases, the two sets of records agree closely. During the autumn, however, the influenza epidemic upset the statistical work in many camps, and in preparing this report we have been confronted by huge discrepancies between the

*A report from the Section of Communicable Diseases, Division of Laboratories and Infectious Disease, prepared under the direction of Col. Frederick F. Russell, and published by permission of the Surgeon General. The writers are printing this as a preliminary report, subject to revision on the receipt of further data and will be grateful to all medical officers for more exact information on matters which came under their observation.

records furnished by the weekly telegraphic reports and the records sent in later by the epidemiologists. As an illustration we submit the following outline: "W. T." referring to the weekly telegraphic reports and "E" meaning the record sent in by the epidemiologist.

CAMP	CASES OF INFLUENZA		CASES OF PNEUMONIA		DEATHS FROM INFLUENZA AND PNEUMONIA	
	W. T.	E.	W. T.	E.	W. T.	E.
Cody	3006	3296	182	823	231	248
Forrest	910	2764	221	527	95	178
MacArthur	8319	7624	479	755	195	200
Dodge	10222	10751	1482	2263	739	856
Pike	14412	12811	969	1824	460	458
Wadsworth	577	1520	717	815	182	—

Pike explains the discrepancy in pneumonia records by the fact that the weekly telegraphic reports were based on records from the base hospital and it was later found that these did not include bronchopneumonia (in accordance with an old order to that effect), while the daily reports covered all pneumonias.

Wadsworth first carried influenza cases as streptococcic infections, which explains the low number under W. T. Later these were all included as influenza.

The discrepancies are usually to be traced to lack of cooperation between the base hospital and the registrar in the camp surgeon's office.

Correspondence with the camps has indicated the greater reliability of the figures from the epidemiologist. We have, therefore, accepted their figures in preference to the weekly telegraphic reports for influenza, pneumonia, and deaths from these two causes during the autumn season. We speak of this to foreshadow any question which may arise in comparing articles on disease conditions in the army which have appeared from time to time or may appear in the future. We have inserted the complete list of the figures which we are using which have been selected after careful examination of the two sources. We do not claim absolute accuracy even after the laborious task of deriving basic figures with which to work. We do feel, however, that by this method of selection we have eliminated most, if not all, of the large discrepancies; and what errors remain may be looked upon as of minor character and not sufficient to alter materially the conclusions drawn therefrom.

Discussion of the influenza epidemic will be found by itself under Sections IV, V and VI.

A. DEATHS, ALL CAUSES

During the summer season, Camp Dodge headed the list of large camps in deaths from all causes with an annual rate per 1000 of 17. This is lower than the highest rate for the previous winter when Pike registered 30.7. Next to Dodge stands Gordon with a death rate of 10.8, and from this point on the rates decline gradually until we come to Syracuse, whose death rate was but 1.9. The records for Syracuse, however, are for two weeks instead of for the twenty-two weeks of the summer season. McArthur likewise is represented only by about seventeen weeks. McClellan, third from the bottom of the table, covers the full record of twenty-two weeks. Its death rate was 2.3.

In Table 9 there are presented the camps in the order of their death rate together with the average strength for the season, number of deaths from disease, number of deaths from causes other than disease, the number of deaths from all causes, and the annual death rate per 1000 for all causes. The relative standing of the camps in mortality is shown graphically in Chart XVI. The most noticeable change on comparing this graph with the graph for the six winter

TABLE 9

DEATHS IN ARMY CAMPS

Five Summer Months—Week Ending April 5, 1918, to August 30, 1918

Annual Death Rate per 1000 for all Troops in U. S..... 5.7

ORDER	CAMP	AVERAGE STRENGTH IN THOUSANDS	NUMBER OF DEATHS FROM DISEASE	NUMBER OF DEATHS FROM CAUSES OTHER THAN DISEASE	NUMBER OF DEATHS FROM ALL CAUSES	ANNUAL DEATH RATE PER 1000 (ALL CAUSES)
1	Dodge	31.2	207	18	225	17.0
2	Gordon	36.4	161	6	167	10.8
3	Pike	36.5	155	5	160	10.3
4	Funston	25.1	104	2	106	10.0
5	Las Casas*	12.8	18	0	18	9.5
6	Custer	26.5	83	12	95	8.5
7	Travis	31.2	94	9	103	7.8
8	Wheeler	23.8	70	7	77	7.6
9	Sherman	32.8	88	3	91	6.5
10	Taylor	34.7	85	4	89	6.1
11	Jackson	33.4	79	3	82	5.8
12	Bowie	19.1	29	18	47	5.8
13	Cody	24.5	55	4	59	5.7
14	Upton	34.5	74	10	84	5.7
15	Grant	36.4	77	5	82	5.3
16	Devens	36.1	71	6	77	5.0
17	Fremont	19.9	34	6	40	4.7
18	Shelby	20.5	28	9	37	4.3
19	Lewis	34.2	52	10	62	4.3
20	Kearny	19.4	20	15	35	4.3
21	Sheridan	15.9	23	4	27	4.0
22	Wadsworth	21.7	29	8	37	4.0
23	Meade	36.3	55	2	57	3.7
24	Lee	42.5	57	7	64	3.6
25	Sevier	19.5	28	2	30	3.6
26	Greene*	7.5	2	0	2	3.5
27	Beauregard	22.1	26	6	32	3.4
28	Greenleaf*	17.7	10	2	12	2.9
29	Johnston	17.6	16	5	21	2.8
30	Dix	46.1	43	10	53	2.7
31	Logan	15.1	13	3	16	2.5
32	Hancock	25.5	20	6	26	2.4
33	MacClellan	15.5	12	3	15	2.3
34	MacArthur*	18.5	11	1	12	2.0
35	Syracuse*	13.5	1	0	1	1.9

*Greenleaf—12 weeks—Week ending June 14 to Aug. 30.
*Las Casas—9 weeks—Week ending July 5 to Aug. 30.
*Greene—3 weeks—Week ending Aug. 16 to Aug. 30.
*Syracuse—2 weeks—Week ending Aug. 23 to Aug. 30.
*MacArthur—17 weeks—Week ending May 10 to Aug. 30.

it is believed explains the situation with respect to our tissue extracts. Disregarding entirely what the toxic agent may be, the complexity of the material is sufficient to rule out any rigid statement concerning solubility, dialysis, or other phenomena of any one substance that may be present. One fact can not be escaped. That is that in the most toxic extracts, analysis showed over one-half of the inorganic constituents of the tissue to be present, and the toxicity rose as the ash value of the extract was increased.

Early in this work we had concluded that the toxic agent of tissue extracts was some stable substance. Anything in the nature of a ferment was excluded by the method of preparation of the extract. In the first place alcohol was used to extract the tissue; ferments are not able to withstand the concentration to which they would have been subjected. Further, some rabbit livers had been saved from time to time as the animals had been used for other purposes. They were preserved by dropping into a large bottle containing absolute alcohol at the start. The most recent of these livers had been in the alcohol for about one year. They were ground and the required amount of water added to the alcohol in which they had been kept to make the volume up to the usual 2 c.c. per gram of tissue. The final extract proved to be the most toxic for liver ever prepared; 1.5 c.c. proving fatal. Secondly, the alcoholic or water extraction liquid was heated during its evaporation, which was carried to relative dryness when alcohol was used and to positive dryness in the case of water, to a higher temperature than ferments can withstand. Then, the extracts themselves were stable on boiling. The extracts showed no deterioration on standing, either at room temperature or in the ice box. Extracts thus kept for three months showed no decrease in toxicity. Whenever an extract was kept for any length of time, it was preserved from bacterial activity by a few drops of trikresol.

The work upon the toxicity of the pure phosphate salts was for the purpose of confirming a well grounded notion as to the toxic agent in the inorganic salts derived from the extract by ignition. Gamgee, Priestly, and Larmuth[36] had noted the differences in the effects of the three forms of phosphoric acid as early as 1877, and had made a special study of the influence of the pyrophosphate salt on heart and circulation. They used rabbits and frogs, and made their injections subcutaneously and intravenously. Gardner and Symes[37] repeated their work in 1910, and confirmed the same. They ascribed the effects of the phosphoric salts to their alkalinity. Starkenstein[34] made a more minute investigation of the effects of the various acid radicals, that it is possible to obtain with the phosphoric acids, due to their polyvalency, and was also led to believe that the alkalinity of the pyrophosphate salts was responsible for their marked activity. Crawford[38] after investigating the ill results of feeding cottonseed meal concluded that the pyrophosphates produced by the method of manufacture were the cause of the deleterious effects. Thus we see that there is ample evidence that the phosphate salts, and especially the pyrophosphates are very toxic substances when introduced into the body by any channel. König[39] states that phosphoric anhydride constitutes from 36 to 48 per cent of the mineral part of

various forms of flesh. The salt that we prepared and subjected to analysis contained 34.8 per cent of phosphoric anhydride. It was necessarily in the pyrophosphate form by reason of the method of its preparation, and was undoubtedly the cause of death in animals injected with a water solution of the salts. The collapsed condition of the lungs of animals dying from injections of either pure phosphate salts or of the salts from the tissue extracts, was a very constant feature. If the statement is acceptable that an anaphylactized animal dies because air can not get out of the lungs, because of the constricted bronchioles, then it would be logical to believe that these animals died because air could not get into the lungs. The dyspnea was very marked, indicating a condition of air hunger exactly analogous to that of animals injected with organ extracts or anaphylatoxin.

The method of preparing the extracts would result in a low protein content. In fact, no satisfactory test for protein was ever made on an extract. The biuret test was negative. In view of the small amount of protein, if any, that was in the extracts, the attempt to immunize rabbits was inevitably doomed to not succeed. The toxic agent of the extracts we believe to have shown to be a chemical entity, and to act as such in the animal body. However, its apparent cumulative effects on repeated injection might be interpreted as a state of sensitization.

SUMMARY AND CONCLUSIONS

The tissues of seven species of animals were extracted with alcohol and found to yield a toxic extract. We believe that the tissue of all animals if similarly extracted would likewise produce a toxic extract.

It was found that the extract of the tissues of the cat, which may be considered representative of all other tissues, contained solids in solution varying from .47 to 1.83 per cent of the original tissue.

The extracts were acid in reaction with the occasional exception of the extract of stomach and intestine. Adjustment of the reaction to neutrality did not alter the toxicity of the extracts.

There was some evidence that toxicity of the extracts could be modified by previous treatment of the animals, especially by fatigue. Inanition was without effect.

Ether does not extract the toxic substance from tissue.

Drying and fine division of rabbit muscle followed by alcoholic extraction gave an extract of negligible toxicity. In view of statements that are to follow, we do not believe that the toxic agent was destroyed by the drying, but rather that it was rendered insoluble in absolute alcohol.

Ignition to a white ash of the solids in extracts prepared by the use of alcohol, shows an inorganic residue of approximately .4 per cent of the tissue. Subsequent solution of this ash to the volume of the extract from which it was obtained, followed by injection, shows it to be always equally toxic, and in some cases more so, than the extract from which it was derived.

It was found that water could be substituted for alcohol as the primary extracting medium, and that a more toxic extract resulted. Further investiga-

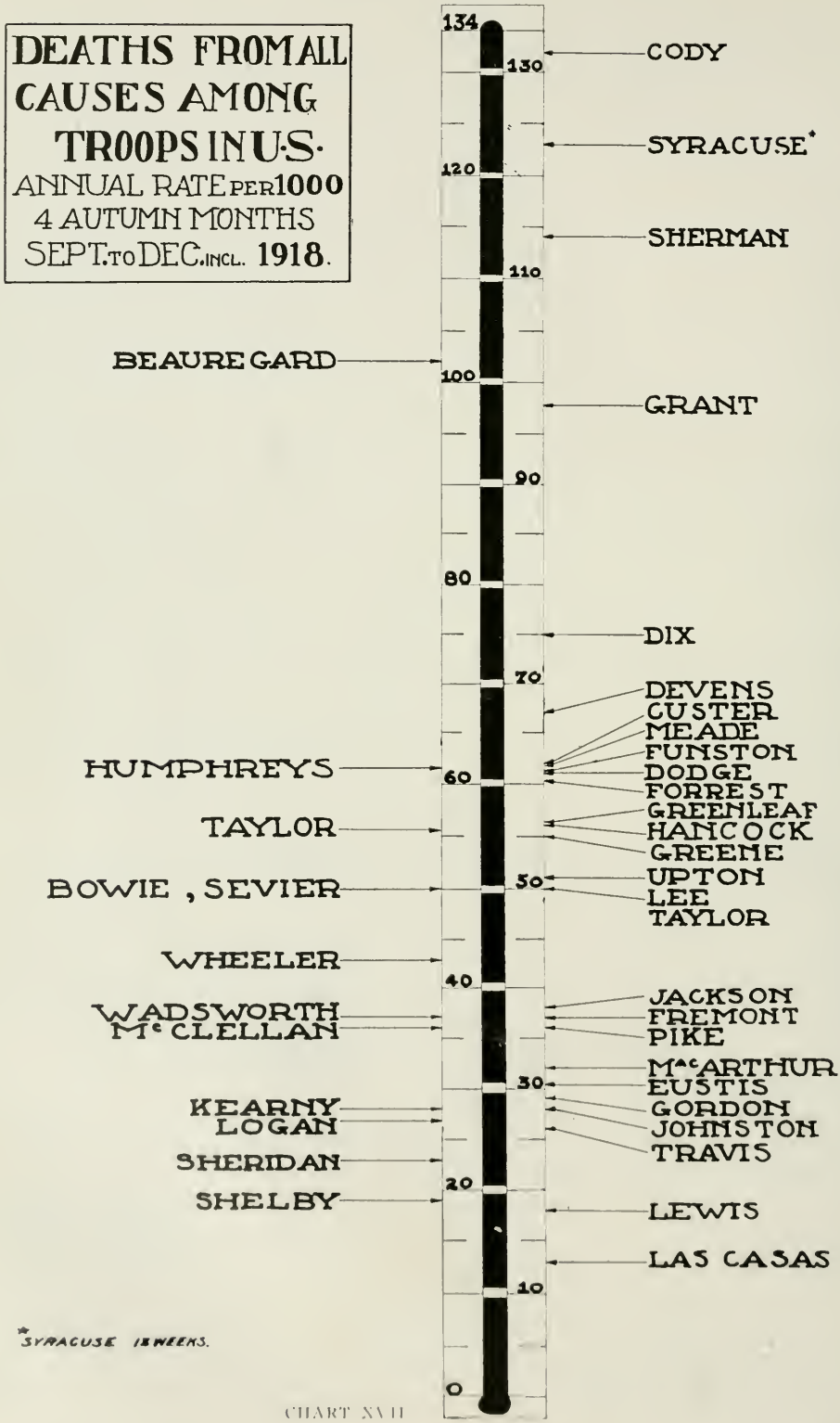
DEATHS FROM ALL CAUSES AMONG TROOPS IN U.S.
ANNUAL RATE PER 1000
4 AUTUMN MONTHS
SEPT. TO DEC. INCL. 1918.
134
130
120
110
100
90
80
70
60
50
40
30
20
10
0
CODY
SYRACUSE*
SHERMAN
BEAUREGARD
GRANT
DIX
DEVENS
CUSTER
MEADE
FUNSTON
DODGE
FORREST
HUMPHREYS
GREENLEAF
TAYLOR
HANCOCK
GREENE
BOWIE, SEVIER
UPTON
LEE
TAYLOR
WHEELER
JACKSON
WADSWORTH
FREMONT
Mc CLELLAN
PIKE
MacARTHUR
EUSTIS
KEARNY
GORDON
LOGAN
JOHNSTON
SHERIDAN
TRAVIS
SHELBY
LEWIS
LAS CASAS
*SYRACUSE 18 WEEKS.

CHART XVII

TABLE 10

DEATHS IN ARMY CAMPS, FOUR AUTUMN MONTHS

Week Ending September 6, 1918, to December 27, 1918

Annual Death Rate per 1000 for All Troops in the U. S..... 48.5.

ORDER	CAMP	AVERAGE STRENGTH IN THOUSANDS	NUMBER OF DEATHS FROM DISEASE	NUMBER OF DEATHS FROM CAUSES OTHER THAN DISEASE	NUMBER OF DEATHS FROM ALL CAUSES	ANNUAL DEATH RATE PER 1000 (ALL CAUSES)
1	Cody	5.9	257	1	258	132.
2	Syracuse*	7.4	225	3	228	123.
3	Sherman	30.9	1147	6	1153	114.
4	Beauregard	13.7	456	3	459	102.
5	Grant	35.0	1119	4	1123	97.8
6	Dix	35.0	858	0	858	75.0
7	Devens	39.5	855	10	865	67.0
8	Meade	42.1	843	8	851	61.9
9	Custer	36.1	692	4	696	61.7
10	Humphreys	24.1	481	3	484	61.5
11	Funston	49.0	976	6	982	61.3
12	Dodge	28.5	767	2	769	61.1
13	Forrest	9.2	180	1	181	60.3
14	Greenleaf	19.9	366	1	367	56.4
15	Hancock	34.0	610	15	625	56.2
16	Taylor	54.9	992	4	996	55.5
17	Greene	16.6	300	0	300	55.3
18	Upton	27.9	458	0	462	50.7
19	Sevier	23.3	378	6	384	50.4
20	Lee	43.8	703	10	713	49.8
21	Bowie	9.8	159	0	159	49.6
22	Wheeler	12.5	174	1	175	42.8
23	Jackson	38.2	465	6	471	37.7
24	Wadsworth	15.3	186	1	187	37.4
25	Fremont	12.9	154	1	155	36.8
26	McClellan	24.6	287	1	288	35.8
27	Pike	44.2	514	1	515	35.7
28	MacArthur	20.7	210	8	218	32.2
29	Eustis	14.0	145	1	146	30.4
30	Gordon	29.3	228	2	230	29.3
31	Johnston	19.7	179	1	180	27.9
32	Kearny	17.5	156	3	159	27.8
33	Logan	14.3	124	2	126	27.0
34	Travis	32.3	265	4	269	25.5
35	Sheridan	22.0	159	3	162	22.5
36	Shelby	12.1	73	2	75	18.9
37	Lewis	35.3	198	6	204	17.7
38	Las Casas	12.8	83	1	84	13.1

*Syracuse—13 weeks—Week ending Sept. 6, to Nov. 29.

We are handicapped in analyzing the disease situation in 1918. In the winter of 1917-18 we knew with considerable accuracy the source of the men at each camp. Since that time men have been shifted about to such an extent and the shifts have become so frequent that it is out of the question to look upon a camp in terms of the sources of the personnel. Our information about troop movements, draft arrivals, and transfers from camp to camp, is incomplete, and much of what we have is unreliable. If this information were available we should be in a much better position to analyze the causes of sickness.

Generally speaking it would seem as though the northern camps had a greater proportion of new men but the differences between northern and southern camps in this respect are by no means clear cut. We believe that the factor of climate and camp location exercises an influence in this latest period that was not evident from the analysis of the first winter season.

B. MEASLES

During the fifteen-month period to which we have repeatedly referred, measles has appeared in severe epidemic form only during the first winter season. There has been no repetition on a large scale of the experience of that time. In the first of the three

TABLE II

MEASLES—FIVE SUMMER MONTHS

Week Ending April 5, 1918, to August 30, 1918

Annual Admission Rate per 1000 for All Troops in U. S....23.2

ORDER	CAMP	AVERAGE STRENGTH IN THOUSANDS	NUMBER OF ADMISSIONS	ANNUAL ADMISSION RATE PER 1000	NUMBER OF DEATHS
1	Pike	36.5	1306	84.0	4
2	Las Casas*	12.8	173	78.1	0
3	Greenleaf*	17.7	253	61.4	2
4	Taylor	34.7	894	60.8	0
5	Gordon	36.4	891	57.8	0
6	Dodge	31.2	750	56.1	0
7	Sevier	19.5	443	53.6	0
8	Jackson	33.4	696	49.3	1
9	Johnston	17.6	276	37.1	0
10	Lee	42.5	640	35.6	0
11	Sheridan	15.9	202	30.0	0
12	Shelby	20.5	221	25.5	0
13	Funston	25.1	251	23.1	0
14	Beauregard	22.1	213	22.7	0
15	Travis	31.2	259	19.1	0
16	Devens	36.1	304	19.1	1
17	Fremont	19.9	151	17.9	1
18	Grant	36.4	266	17.2	0
19	Kearny	19.4	132	16.2	0
20	Custer	26.5	182	16.2	0
21	Logan	15.1	102	16.1	0
22	Wadsworth	21.7	143	15.6	1
23	Upton	34.5	216	14.8	1
24	Cody	24.5	150	14.5	0
25	Lewis	34.2	195	13.5	0
26	MacArthur*	15.5	66	13.0	0
27	Sherman	32.8	170	12.2	5
28	Dix	46.1	237	12.0	0
29	Greene*	7.5	6	10.4	0
30	Meade	36.3	138	9.0	0
31	McClellan	18.5	63	8.1	0
32	Hancock	25.5	43	4.0	0
33	Bowie	19.1	30	3.7	0
34	Syracuse*	13.5	1	1.9	0

*Las Casas—9 weeks—Week ending July 5 to Aug. 30.
*Greenleaf—12 weeks—Week ending June 14, to Aug. 30.
*MacArthur—17 weeks—Week ending May 10, to Aug. 30.
*Syracuse—2 week—Week ending Aug. 23, to Aug. 30.
*Greene—3 weeks—Week ending Aug. 16, to Aug. 30.

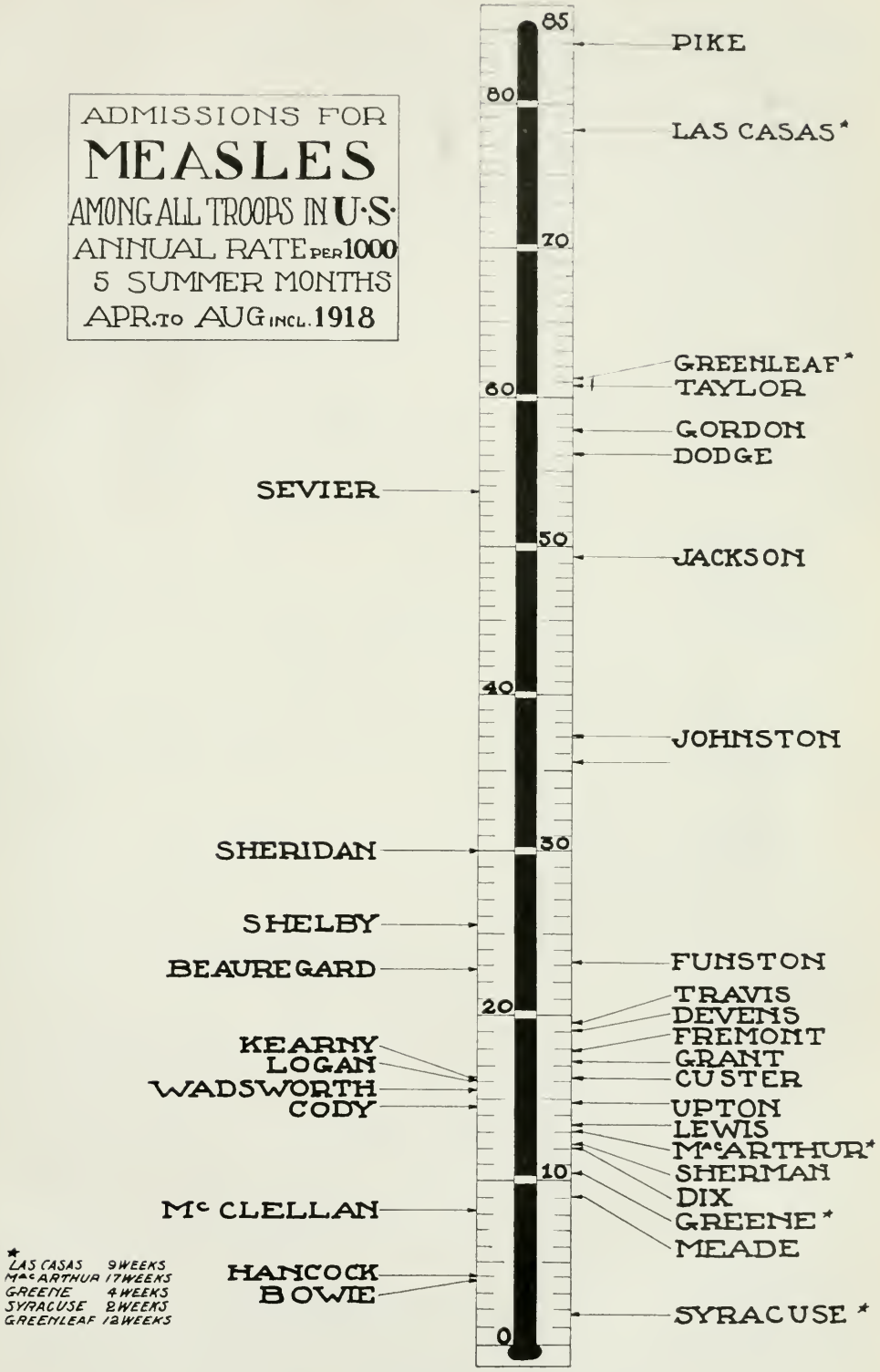
ADMISSIONS FOR
MEASLES
AMONG ALL TROOPS IN U·S·
ANNUAL RATE PER 1000
5 SUMMER MONTHS
APR. TO AUG INCL. 1918
85
80
70
60
50
40
30
20
10
0
PIKE
LAS CASAS*
GREENLEAF*
TAYLOR
GORDON
DODGE
SEVIER
JACKSON
JOHNSTON
SHERIDAN
SHELBY
BEAUREGARD
FUNSTON
TRAVIS
DEVENS
FREMONT
GRANT
CUSTER
KEARNY
LOGAN
WADSWORTH
CODY
UPTON
LEWIS
Mc ARTHUR*
SHERMAN
DIX
GREENE*
MEADE
Mc CLELLAN
HANCOCK
BOWIE
SYRACUSE*
* LAS CASAS 9 WEEKS
Mac ARTHUR 17 WEEKS
GREENE 4 WEEKS
SYRACUSE 2 WEEKS
GREENLEAF 12 WEEKS

CHART XVIII.

seasons, Pike had an annual admission rate for measles of 390 per 1000. During the summer season Pike still remained at the top of the list, but with a rate of 84. In the autumn season Las Casas stands first with a rate of 77.7 and Pike occupies fourth place with a rate of 64.8 (See Table 11 and Chart XVIII).

As has been pointed out elsewhere in this report, the most remarkable diminution of the measles incidence is to be found at Camp Wheeler, not a single case being reported for the entire season. Viewed in the light of Wheeler's record during the preceding winter when the measles morbidity rate was 297, Wheeler standing in third place among all the large camps, it is truly astounding that such an abrupt cutting off of measles incidence is possible. Measles, probably more than any other disease, runs true to form in picking the nonimmunes. A previous attack is apparently the only effective guarantee against measles in later life. Measles permeated Wheeler so effectively as to pick every susceptible person. When the epidemic was over there was no one left untouched. In the months to come there were practically no new increments entering Wheeler and consequently no fresh material introduced.

The experience at Wheeler is duplicated by a number of other camps where an epidemic raged during the fall of 1917. Bowie with a rate of 374 in the winter season dropped to a rate of 3.7 for the summer. Jackson with a rate of 230 fell off to 49.3, and Beauregard with a rate of 256 fell to 22.7. Las Casas is the only camp in the entire list which showed measles in epidemic form similar to the outbreaks that occurred in the fall of 1917. This was a newly formed camp of susceptible individuals.

There was a great deal of measles endemic at Camp Dodge due to the acquisition of new personnel, but the morbidity never reached the epidemic proportions of the previous winter. Of 525 cases occurring during the twelve weeks from June 1 to September 1, there is definite evidence that many men contracted the disease en route to camp. The cases during the summer were relatively mild, and an unusual feature was the high proportion of the hemorrhagic types.

Measles at Grant was sporadic and confined for the most part to recruits.

Devens reports that practically all measles during August was brought into camp by recruits. Major Woolley, epidemiologist, believes more intimate contact during the winter stimulates the spread of measles, whereas, during the summer with an equal number of foci and susceptibles the spread is slow.

The autumn season of 1918 differed from that of the previous year in that there were no camps that had recently been entirely filled from civilian life. It is this fact as much if not more than any other that accounts for the nonappearance of measles epidemics. (See Table 12 and Chart XIX.) Las Casas was the nearest likeness to a virgin camp as it had been in operation but a few weeks when measles appeared. Measles broke out in August and continued throughout September. If all of these cases had occurred within the autumn season the rate for Las Casas would have compared with some of the camps of the fall of 1917. As it was the epidemic at Las Casas was divided by the seasons, and the rates are consequently reduced in size. MacArthur, which stood next to Las Casas in measles incidence, can not be said to have had an epidemic, for the cases were spread out over the entire autumn season, on only one occasion exceeding 48 cases per week, this being in the second week of October, when 68 cases were reported. Shelby had a great deal of measles during August and September, and its incidence is reduced in consequence of our arbitrary division of the seasons. Measles has been endemic at Pike throughout the entire fifteen months. It assumed epidemic proportions only during the last week in October, 240 cases being reported in one week. At Funston, likewise, measles has been present almost continuously, the cases increasing appreciably during September. Bowie is the only camp in which measles did not appear during the autumn season.

The deaths attributed to measles have been few. In this respect, however, our report will differ from the Annual Report of the Surgeon General where measles cases which terminated fatally in pneumonia will be registered as deaths from measles. In the weekly reports it is customary to charge a measles-pneumonia death to pneumonia.

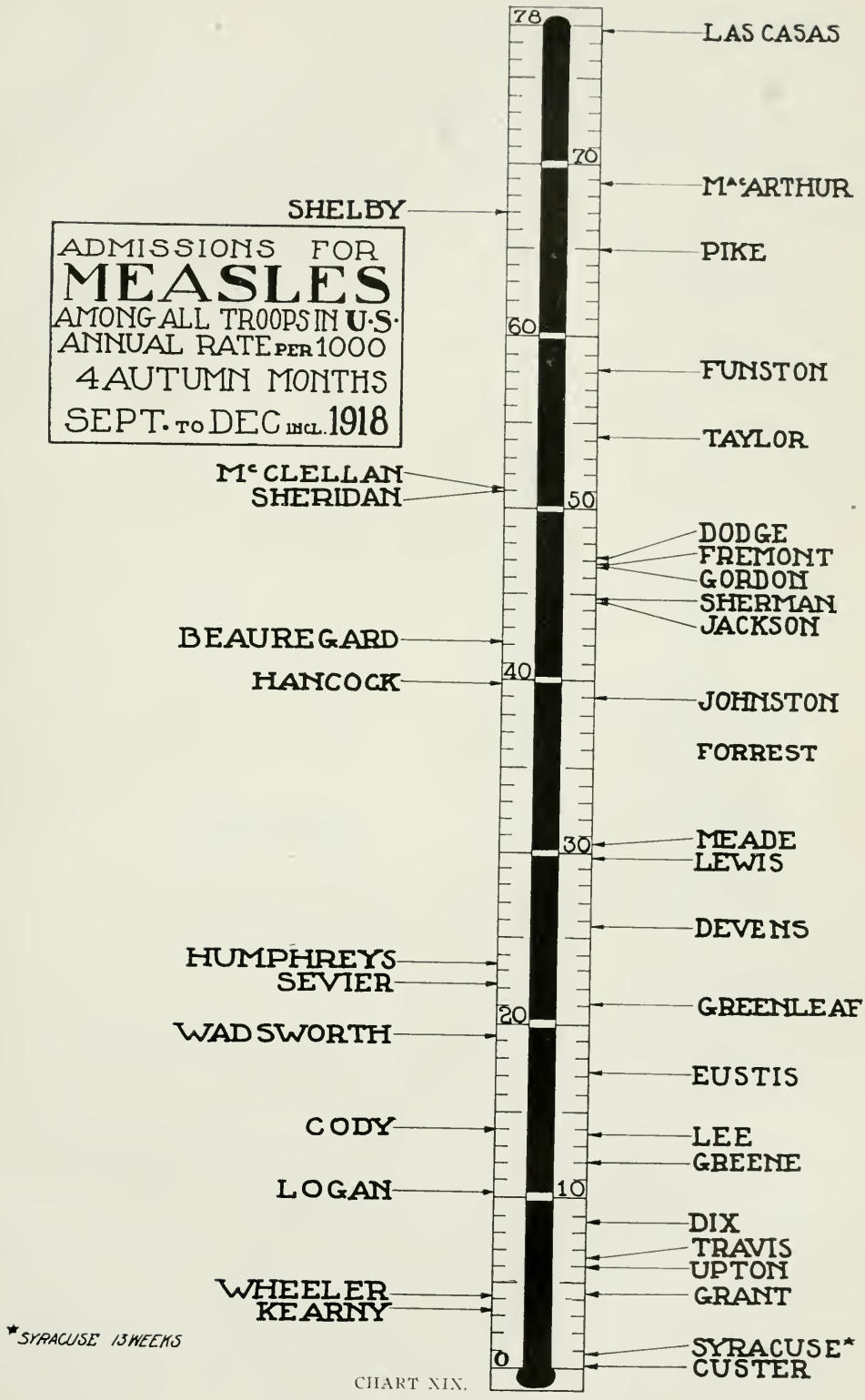
ADMISSIONS FOR
MEASLES
AMONG ALL TROOPS IN U.S.
ANNUAL RATE PER 1000
4 AUTUMN MONTHS
SEPT. TO DEC INCL. 1918
78
70
60
50
40
30
20
10
0
LAS CASAS
Mac ARTHUR
SHELBY
PIKE
FUNSTON
TAYLOR
Mc CLELLAN
SHERIDAN
DODGE
FREMONT
GORDON
SHERMAN
JACKSON
BEAUREGARD
HANCOCK
JOHNSTON
FORREST
MEADE
LEWIS
DEVENS
HUMPHREYS
SEVIER
GREENLEAF
WADSWORTH
EUSTIS
CODY
LEE
GREENE
LOGAN
DIX
TRAVIS
UPTON
WHEELER
KEARNY
GRANT
SYRACUSE*
CUSTER
*SYRACUSE 13 WEEKS

CHART XIX.

Table 12

Measles—Four Autumn Months

Week Ending September 6, to December 27, 1918

Annual Admission Rate per 1000 for All Troops in U. S.....24.1

ORDER	CAMP	AVERAGE STRENGTH IN THOUSANDS	NUMBER OF ADMISSIONS	ANNUAL ADMISSION RATE PER 1000	NUMBER OF DEATHS
1	Las Casas	12.8	325	77.7	0
2	MacArthur	20.7	465	68.7	1
3	Shelby	12.1	265	67.0	0
4	Pike	44.2	938	64.8	0
5	Funston	49.0	928	58.0	1
6	Taylor	54.9	973	54.2	1
7	McClellan	24.6	411	51.1	0
8	Sheridan	22.0	351	48.9	0
9	Dodge	28.5	438	47.1	1
10	Fremont	12.9	197	46.7	0
11	Gordon	29.3	446	46.6	2
12	Sherman	30.9	441	44.7	1
13	Jackson	38.2	556	44.5	1
14	Beauregard	13.7	190	42.4	0
15	Hancock	34.0	443	39.8	0
16	Johnston	19.7	251	39.0	0
17	Forrest	9.2	108	36.0	0
18	Meade	42.1	419	30.5	4
19	Lewis	35.3	343	29.7	1
20	Devens	39.5	330	25.6	0
21	Humphreys	24.1	185	23.5	1
22	Sevier	23.3	170	22.3	0
23	Greenleaf	19.9	138	21.2	2
24	Wadsworth	15.3	97	19.4	0
25	Eustis	14.0	79	17.2	0
26	Cody	5.9	27	14.0	0
27	Lee	43.8	196	13.7	0
28	Greene	16.6	65	12.0	0
29	Logan	14.3	48	10.3	0
30	Dix	35.0	101	8.8	0
31	Travis	32.3	70	6.6	1
32	Upton	27.9	56	6.1	0
33	Grant	35.0	49	4.3	0
34	Wheeler	12.5	17	4.2	0
35	Kearny	17.5	19	3.3	0
36	Syracuse*	7.4	2	.8	0
37	Custer	36.1	2	.2	0

*Syracuse 12 weeks. Week ending Sept. 6, to Nov. 29.

Much has been said of the importance of measles as a predisposing cause of pneumonia, particularly bronchopneumonia. Of 235 cases of measles at Cody during the winter of 1917-18, 77 or 33 per cent developed either bronchopneumonia or lobar pneumonia. Of these about 42 per cent died, which is a high pneumonia fatality.

As a rule pneumonia follows measles with far less frequency than is indicated at Cody. The Surgeon General's Report for 1918 gives 48,900 measles admissions and 2,075 pneumonias resulting therefrom. This indicates that 4.25 per cent of measles cases terminated in pneumonia. This figure seems so small as to indicate a lack of association between the two. Nevertheless this association exists. Among 510,100 men who did not have measles in 1918 there occurred 8,432 cases of pneumonia. The percentage pneumonia incidence is thus 1.65. We may interpret these percentages in the following manner

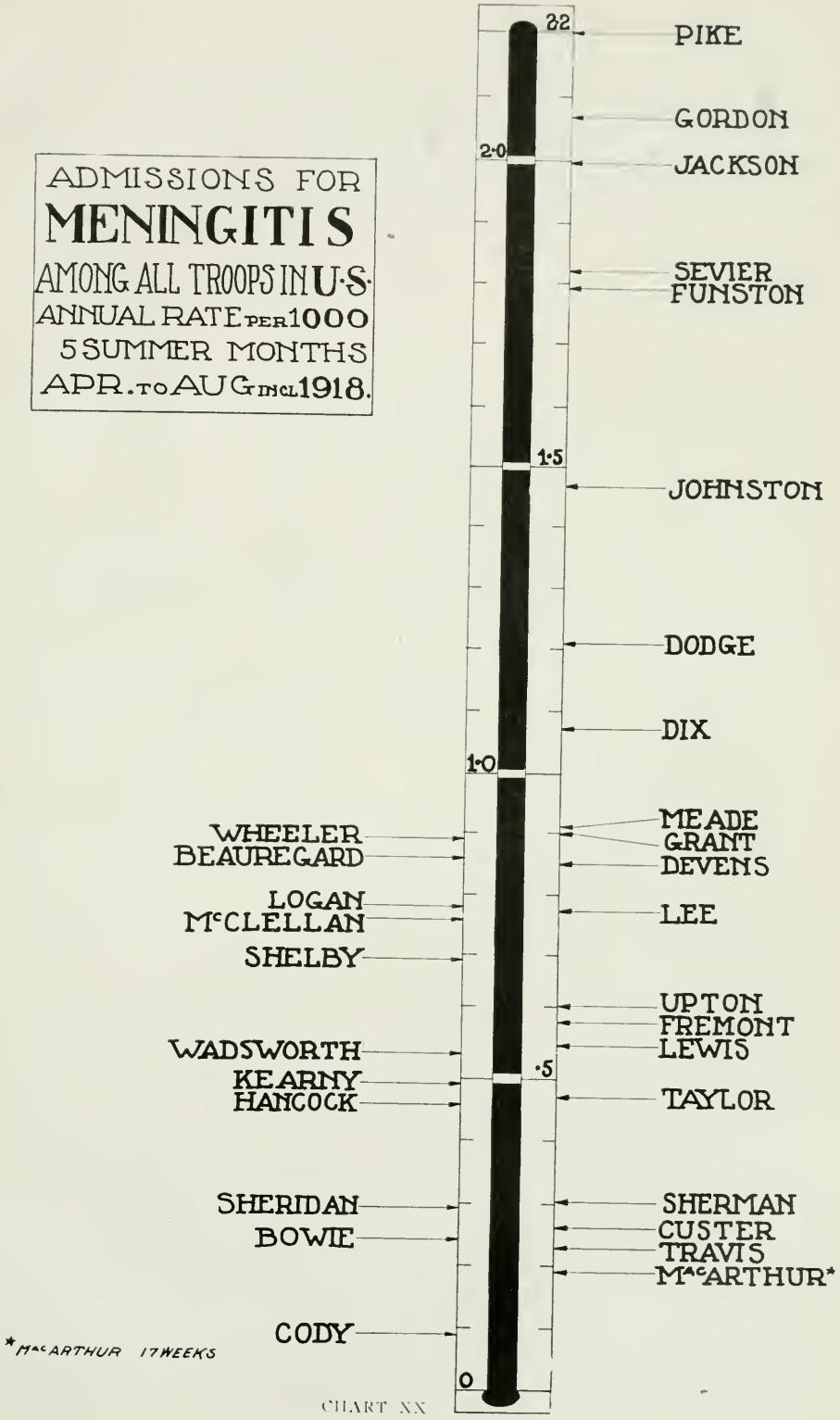
ADMISSIONS FOR
MENINGITIS
AMONG ALL TROOPS IN U.S.
ANNUAL RATE PER 1000
5 SUMMER MONTHS
APR. TO AUG INCL 1918.
2·2
2·0
1·5
1·0
·5
0
PIKE
GORDON
JACKSON
SEVIER
FUNSTON
JOHNSTON
DODGE
DIX
MEADE
GRANT
DEVENS
LEE
UPTON
FREMONT
LEWIS
TAYLOR
SHERMAN
CUSTER
TRAVIS
MacARTHUR*
WHEELER
BEAUREGARD
LOGAN
McCLELLAN
SHELBY
WADSWORTH
KEARNY
HANCOCK
SHERIDAN
BOWIE
CODY
*MacARTHUR 17 WEEKS

CHART XX

Where one man without measles has pneumonia, two to three (2.6) men with measles will have pneumonia.

Measles thus predisposes to pneumonia.

Granted that measles predisposes to pneumonia, we must next appreciate the seriousness of what this means. It is much more than the ratio of 1 to 2.6 indicates. It is not merely that where one nonmeasles case has pneumonia, from two to three measles cases have pneumonia. It is this: the nonmeasles case is more likely to recover from pneumonia once he has it than is the measles case. Thus of 2,075 pneumonia cases following measles, 888, or 42.7 per cent, died. Of 8,432 pneumonia cases not following measles, 949 or only 11.3 per cent died. Measles thus not only predisposes to pneumonia, it predisposes to *fatal pneumonia.*

We may express this relationship of measles and pneumonia as brought out in the 1917 Report, in the following illustrative manner:

OF EVERY 1000 MEN WITH MEASLES, 44 HAVE PNEUMONIA AND 19 DIE.
OF EVERY 1000 MEN WITHOUT MEASLES, 17 HAVE PNEUMONIA AND 2 DIE.
THUS A PERSON WITH MEASLES IS TEN TIMES AS LIKELY TO DIE AS A PERSON WITHOUT MEASLES.

C. MENINGITIS

Meningitis prevailed most extensively during the winter months December, January, and February, 1917-18. The weekly rates from April to December, 1918, have approached the previous winter rates in only two weeks, namely, in the last weeks of October, or just following the peak of the influenza epidemic.

During the summer period meningitis was reported from 31 of the 38 large camps, the admissions varying from 1 to 34 for the period. Camp Pike stands at the top of the list with an annual admission rate per thousand of 2.2. Pike is followed closely by Gordon, Sevier and Funston. The rates from this point in the table decrease gradually to 0. (See Table 13 and Chart XX.)

In Table 13 there are also given the number of deaths from meningitis in each camp. From the death and admission columns there has been computed the case mortality. In two instances, there are more deaths than cases. Where the deaths exceed the cases, it is evident that the cases were not reported. For two-thirds of this table the number of cases are so few that the computation of the case mortality is not significant. For the first ten camps we see that the case mortality runs from 0 to 79 per cent. Grant had a case mortality of 79 per cent, Dodge 63 per cent and Sevier 53 per cent. On the other hand, Johnston had 11 cases but no deaths, and Meade a case mortality of but 21 per cent. For the other camps the case mortality runs from 38 per cent to 53 per cent.

During the autumn months meningitis increased, Beauregard heading the table for the season with an admission rate of 4.9. (See Table 14 and Chart XXI.) At least seven camps had rates higher than the highest rate for the summer season. During the winter of 1917-18 meningitis was most prevalent at Camps Jackson, Beauregard, and Funston. During the summer season these three camps were within the first twelve in the table, and during the autumn season the same three camps were in the first thirteen of the table. For the other camps there is apparently no persistent rate as the standing of each camp fluctuates with the season. This table does not indicate any relation between influenza and meningitis. Of the first ten camps in the meningitis table, Beauregard, Devens and Meade stood high as respects influenza, but the other camps were not unusually high. This is contrary to the experience as shown in Chart XIV, where meningitis increases at the same time as influenza. A number of the camps speak of influenza increasing the meningitis incidence.

Taking the first nineteen camps in the autumn table, all of which have at least a dozen cases of meningitis, we find the case mortality varies from 6 per cent at Sherman to 55 per cent at Pike. At Funston where meningitis was more or less prevalent throughout the

TABLE 13

MENINGITIS—FIVE SUMMER MONTHS

Week Ending April 5, 1918, to August 30, 1918

Annual Admission Rate per 1000 for All Troops in U. S.....0.83

ORDER	CAMP	AVERAGE STRENGTH IN THOUSANDS	NUMBER OF ADMISSIONS	ANNUAL ADMISSION RATE PER 1000	NUMBER OF DEATHS	PER CENT CASE MORTALITY
1	Pike	36.5	34	2.2	15	44.
2	Gordon	36.4	32	2.1	15	47.
3	Jackson	33.4	28	2.0	12	43.
4	Sevier	19.5	15	1.8	8	53.
5	Funston	25.1	19	1.8	9	47.
6	Johnston	17.6	11	1.5	0	0.
7	Dodge	31.2	16	1.2	10	63.
8	Dix	46.1	21	1.1	8	38.
9	Meade	36.3	14	.9	3	21.
10	Grant	36.4	14	.9	11	79.
11	Wheeler	23.8	9	.9	7	78.
12	Beauregard	22.1	8	.9	5	63.
13	Devens	36.1	13	.8	4	31.
14	Logan	15.1	5	.8	0	0.
15	Lee	42.5	14	.8	2	14.
16	McClellan	18.5	6	.8	2	33.
17	Shelby	20.5	6	.7	3	50.
18	Upton	34.5	9	.6	6	67.
19	Fremont	19.9	5	.6	1	20.
20	Lewis	34.2	8	.5	5	63.
21	Wadsworth	21.7	5	.5	5	100.
22	Kearny	19.4	4	.5	3	75.
23	Taylor	34.7	7	.5	4	57.
24	Hancock	25.5	5	.5	1	20.
25	Sherman	32.8	4	.3	4	100.
26	Sheridan	15.9	2	.3	0	0.
27	Custer	26.5	3	.3	5	100.+
28	Bowie	19.1	2	.2	1	50.
29	Travis	31.2	3	.2	3	100.
30	MacArthur*	15.5	1	.2	2	100.+
31	Cody	24.5	1	.1	1	100.

*MacArthur—17 weeks—Week ending May 10, to Aug. 30.

fifteen months, the case mortality was 50 per cent; at Jackson it was 31 per cent and at Beauregard, 18 per cent.

Meningitis is a disease apparently to which few people are susceptible. It has not occurred epidemically in the army. The cases are sporadic. Of 12 cases at Cody during 1917-18 not one was associated with any other.

Meningitis is kept alive by the existence of carriers, people who may or may not have had the disease. At Cody there were found among 20,000 men in the spring of 1918, 268 carriers. In no instance did these men give a previous history of meningitis and yet they were dangerous to their comrades for all of the active meningitis cases admitted close association with one or more of the carriers.

One hundred and thirty-two cases of meningitis occurred at Beauregard from September, 1917, to May, 1918. These were widely distributed over the camp and occurred quite independently of each other.

At Lewis, for the 15 months from October, 1917, to December, 1918, there were 54 cases of cerebrospinal meningitis. In the search for carriers 18,998 men were cultured, among whom were found 273 positives or 1.4 per cent. The ratio of carriers to cases is

Table 14

Meningitis—Four Autumn Months

Week Ending September 6, 1918, to December 27, 1918

Annual Admission Rate per 1000 for All Troops in U. S.....1.3

ORDER	CAMP	AVERAGE STRENGTH IN THOUSANDS	NUMBER OF ADMISSIONS	ANNUAL ADMISSION RATE PER 1000	NUMBER OF DEATHS	PER CENT CASE MORTALITY
1	Beauregard	13.7	22	4.9	4	18.
2	Taylor	54.9	81	4.5	20	25.
3	Sevier	23.3	31	4.1	9	29.
4	Jackson	38.2	49	3.9	15	31.
5	Greene	16.6	17	3.2	7	41.
6	Pike	44.2	38	2.6	21	55.
7	Devens	39.5	30	2.3	9	30.
8	McClellan	24.6	17	2.1	2	12.
9	Meade	42.1	27	1.9	12	44.
10	Logan	14.3	8	1.7	3	38.
11	Greenleaf	19.9	11	1.7	1	9.
12	Sherman	30.9	16	1.6	2	6.
13	Funston	49.0	24	1.5	12	50.
14	Gordon	29.3	15	1.5	7	47.
15	Humphreys	24.1	12	1.5	4	33.
16	Lee	43.8	18	1.2	7	39.
17	Lewis	35.3	14	1.2	4	29.
18	Dix	35.0	14	1.2	5	36.
19	Travis	32.3	12	1.1	2	17.
20	Cody	5.9	2	1.0	2	100.
21	Johnston	19.7	6	.9	2	33.
22	Hancock	34.0	10	.9	4	40.
23	Bowie	9.8	3	.9	2	67.
24	Wadsworth	15.3	4	.8	0	0.
25	MacArthur	20.7	4	.6	2	50.
26	Dodge	28.5	6	.6	2	33.
27	Fremont	12.9	2	.5	0	0.
28	Shelby	12.1	2	.5	1	50.
29	Wheeler	12.5	2	.5	2	100.
30	Upton	27.9	5	.5	2	40.
31	Custer	36.1	5	.4	3	60.
32	Grant	35.0	3	.3	2	67.
33	Sheridan	22.0	2	.3	1	50.
34	Eustis	14.0	1	.2	0	0.

five to one. Strange to say, no clinical cases developed among carriers and of 29 clinical cases cultured, but 7 showed the meningococcus in nasopharyngeal swabs. It was the general opinion that the cases fell off as the cultural method of control followed by isolation of carriers was put into effect. Again we are struck by the nonepidemic nature of the disease from the fact that with three exceptions no secondary cases developed within an organization.

Six cases of meningitis occurred at Devens during May and June. A brief description of these cases will be of interest in showing the absence of contact infection between them.

May 5.—Pvt. A, 3 Bn. Depot Brigade; just entered service; admitted to hospital for mumps four days after being drafted; no possibility of contact with meningitis in camp.

May 25.—Pvt. B, Medical Detachment, Base Hospital; three weeks in service; member of Co. 1, 1st. Bn., Depot Brigade, which was in quarantine; became sick about four

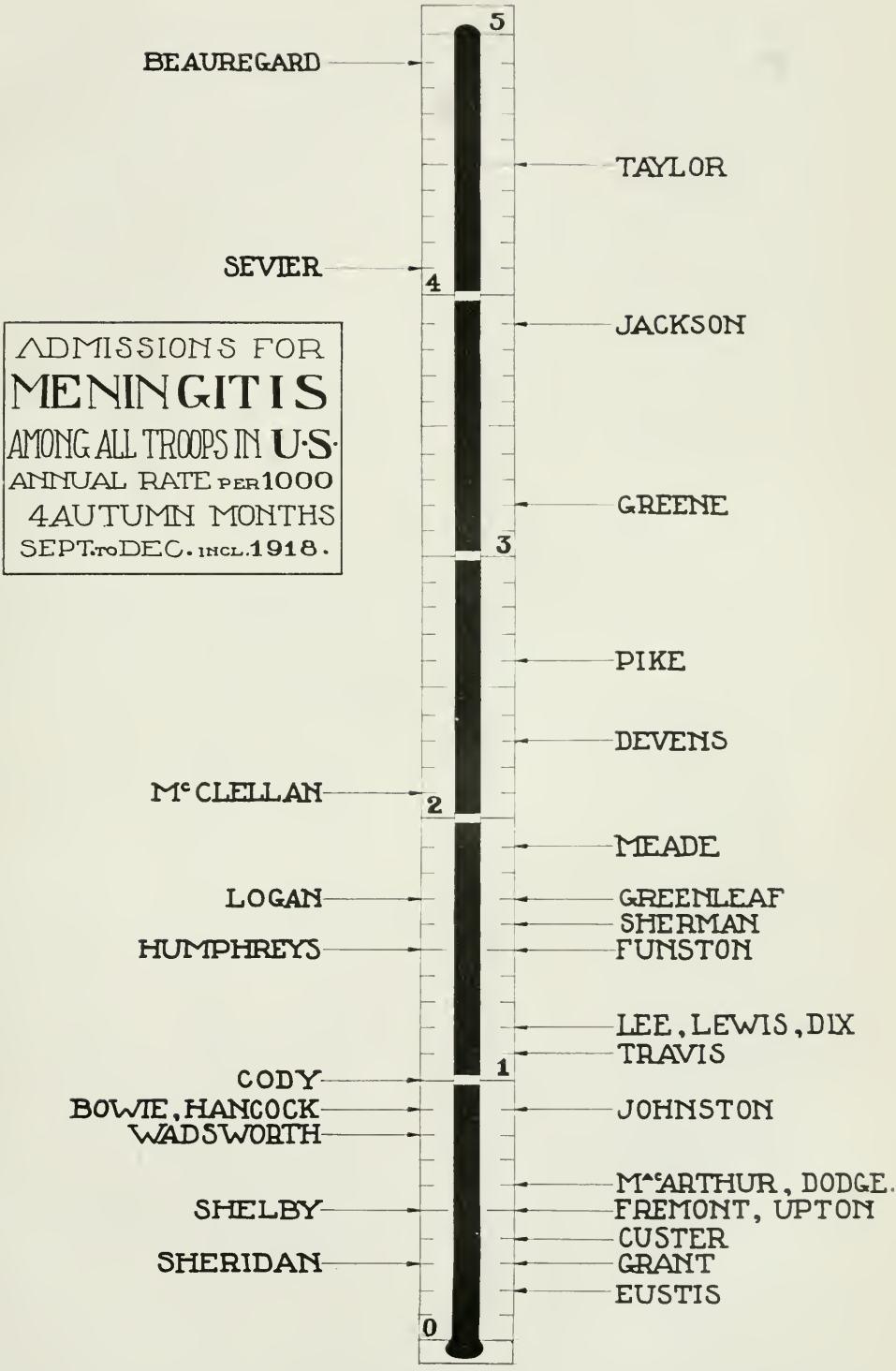
ADMISSIONS FOR
MENINGITIS
AMONG ALL TROOPS IN U·S·
ANNUAL RATE PER 1000
4 AUTUMN MONTHS
SEPT. to DEC. INCL. 1918.
5
4
3
2
1
0
BEAUREGARD
TAYLOR
SEVIER
JACKSON
GREENE
PIKE
DEVENS
McCLELLAN
MEADE
LOGAN
GREENLEAF
SHERMAN
HUMPHREYS
FUNSTON
LEE, LEWIS, DIX
TRAVIS
CODY
BOWIE, HANCOCK
WADSWORTH
JOHNSTON
McARTHUR, DODGE.
SHELBY
FREMONT, UPTON
CUSTER
SHERIDAN
GRANT
EUSTIS

CHART XXI.

days after quarantine at which time he was with Medical Detachment at Base Hospital; no apparent opportunity for contact with meningitis.

June 1.—Pvt. C, (colored), Co. 3, 519 E. S. Bn., in hospital May 14-24 with mumps; no opportunity for contact with meningitis in hospital or quarters.

June 4.—Pvt. D, (colored), D. Co., 519 E. S. Bn.; two months' service; no other cases in his company and Pvt. C. (above) though a member of the same battalion lived in the second barracks distant.

June 4.—Lt. E., Co. D., 302 Inf.; 10 months' service; low sick rate in his company; in Boston on leave May 25; at rifle range about this time and also June 1.

June 4.—Lt. F., Hdq. Co., 303 Inf.; eight months' service; quartered with four other men in small building near stables for three weeks before taking ill; roommates well; on leave to Boston a week before illness.

There was no intimacy between any of these men. The most that can be said is that the majority of these and previous cases have appeared in the Depot Brigade and Service Battalions. There is more overcrowding in these units than elsewhere in camp.

It is evident from this Devens incident that few people are susceptible to meningitis. There were one or more carriers in camp, who spread infection only as they came in contact with susceptible individuals. The victim did not need to be a roommate, a

Table 15

Scarlet Fever—Five Summer Months

Week Ending April 5, 1918, to August 30, 1918

Annual Admission Rate per 1000 for All Troops in U. S..... 3.4

ORDER	CAMP	AVERAGE STRENGTH IN THOUSANDS	NUMBER OF ADMISSIONS	ANNUAL ADMISSION RATE PER 1000	NUMBER OF DEATHS
1	Lewis	34.2	170	11.7	0
2	Dodge	31.2	138	10.4	0
3	Sherman	32.8	112	8.1	1
4	Custer	26.5	74	6.6	0
5	Logan	15.1	38	6.0	2
6	Dix	46.1	105	5.2	0
7	Kearny	19.4	39	4.8	0
8	Funston	25.1	40	3.8	0
9	Grant	36.4	58	3.8	0
10	Upton	34.5	51	3.5	0
11	Sheridan	15.9	15	2.2	0
12	Greenleaf*	17.7	8	1.9	0
13	Devens	36.1	29	1.9	0
14	Johnston	17.6	13	1.8	0
15	Pike	36.5	25	1.6	0
16	Sevier	19.5	13	1.6	0
17	Fremont	19.9	9	1.1	0
18	MacArthur*	15.5	5	1.0	0
19	Wadsworth	21.7	9	1.0	0
20	Gordon	36.4	15	1.0	0
21	Meade	36.3	14	.9	0
22	Taylor	34.7	13	.9	0
23	Travis	31.2	8	.6	0
24	Shelby	20.5	4	.5	1
25	Hancock	25.5	5	.5	0
26	Jackson	33.4	4	.3	0
27	Cody	24.5	3	.3	0
28	Lee	42.5	1	.05	0

*Greenleaf—12 weeks—Week ending June 14, to Aug. 30.
*MacArthur—17 weeks—Week ending May 10, to Aug. 30.

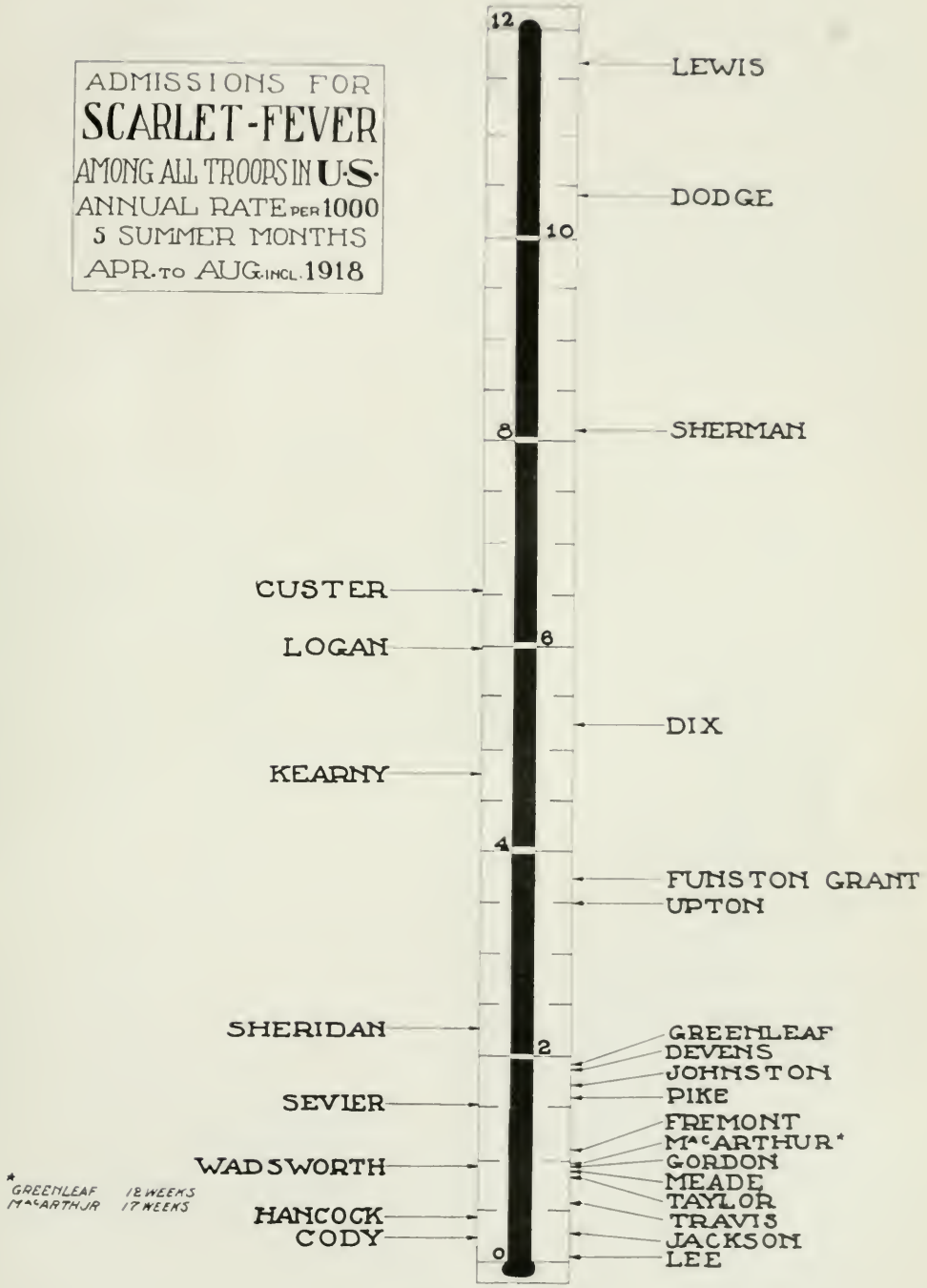
ADMISSIONS FOR
SCARLET-FEVER
AMONG ALL TROOPS IN U.S.
ANNUAL RATE PER 1000
5 SUMMER MONTHS
APR. TO AUG. INCL. 1918
12
10
8
6
4
2
0
LEWIS
DODGE
SHERMAN
CUSTER
LOGAN
DIX
KEARNY
FUNSTON GRANT
UPTON
SHERIDAN
GREENLEAF
DEVENS
JOHNSTON
SEVIER
PIKE
FREMONT
MacARTHUR*
WADSWORTH
GORDON
MEADE
TAYLOR
HANCOCK
TRAVIS
CODY
JACKSON
LEE
* GREENLEAF 18 WEEKS
MacARTHUR 17 WEEKS

CHART XXII.

messmate, or a member of the same company. Contact among soldiers is not limited to the four walls of a tent. This point should be borne in mind by those who advocate elaborate precautions in segregating men in their quarters. After all it is the infected hand and the careless mouth which are responsible for the trouble and these members can operate on the street, in the post exchange, at drill and at play. Until the simple rules of personal hygiene are taken seriously, other preventive activities may be considered woefully inadequate.

D. SCARLET FEVER

Scarlet fever during the winter months of 1917-18 was most prevalent at Camp Pike whose rate at this time was almost twice that of any other camp. The morbidity rates from Lewis, Kearny, Dodge, and Sherman were all above 12 per 1000. The highest rate for the summer season was 11.7 at Camp Lewis. Twenty-eight camps out of thirty-eight reported scarlet fever during the summer season. The scarlet fever data are presented in Table 15, and are illustrated in Chart XXII.

In the autumn of 1918 the only marked increase in scarlet fever was at Camps Han-

TABLE 16

SCARLET FEVER—FOUR AUTUMN MONTHS

Week Ending September 6, 1918, to December 27, 1918

Annual Admission Rate per 1000 for All Troops in U. S.....2.2

ORDER	CAMP	AVERAGE STRENGTH IN THOUSANDS	NUMBER OF ADMISSIONS	ANNUAL ADMISSION RATE PER 1000	NUMBER OF DEATHS
1	Hancock	38.0	416	36.7	0
2	Cody	5.9	48	24.8	0
3	Funston	49.0	102	6.1	0
4	Taylor	54.9	65	3.6	0
5	Grant	35.0	31	2.7	2
6	Dodge	28.5	26	2.6	0
7	Lewis	35.3	24	2.1	0
8	Custer	36.1	17	1.4	0
9	Sherman	30.9	11	1.1	0
10	Sevier	23.3	8	1.0	1
11	Eustis	14.0	4	.9	0
12	Pike	44.2	13	.9	0
13	Wadsworth	15.3	4	.8	0
14	Syracuse*	7.4	1	.4	0
15	Greenleaf	19.9	4	.6	0
16	Meade	42.1	8	.6	1
17	Devens	39.5	7	.5	0
18	Jackson	38.2	5	.4	0
19	Sheridan	22.0	3	.4	0
20	Lee	43.8	4	.3	0
21	Johnston	19.7	2	.3	0
22	Gordon	29.3	3	.3	0
23	Dix	25.0	4	.3	0
24	MacArthur	20.7	2	.3	0
25	Kearny	17.5	2	.3	0
26	Upton	27.9	2	.2	0
27	Travis	32.3	1	.2	1
28	Shelby	12.1	1	.2	0
29	McClellan	24.6	2	.2	0
30	Logan	14.3	1	.2	0
31	Greene	16.6	1	.2	0

*Syracuse 13 weeks Week ending Sept. 6, to Nov. 29.

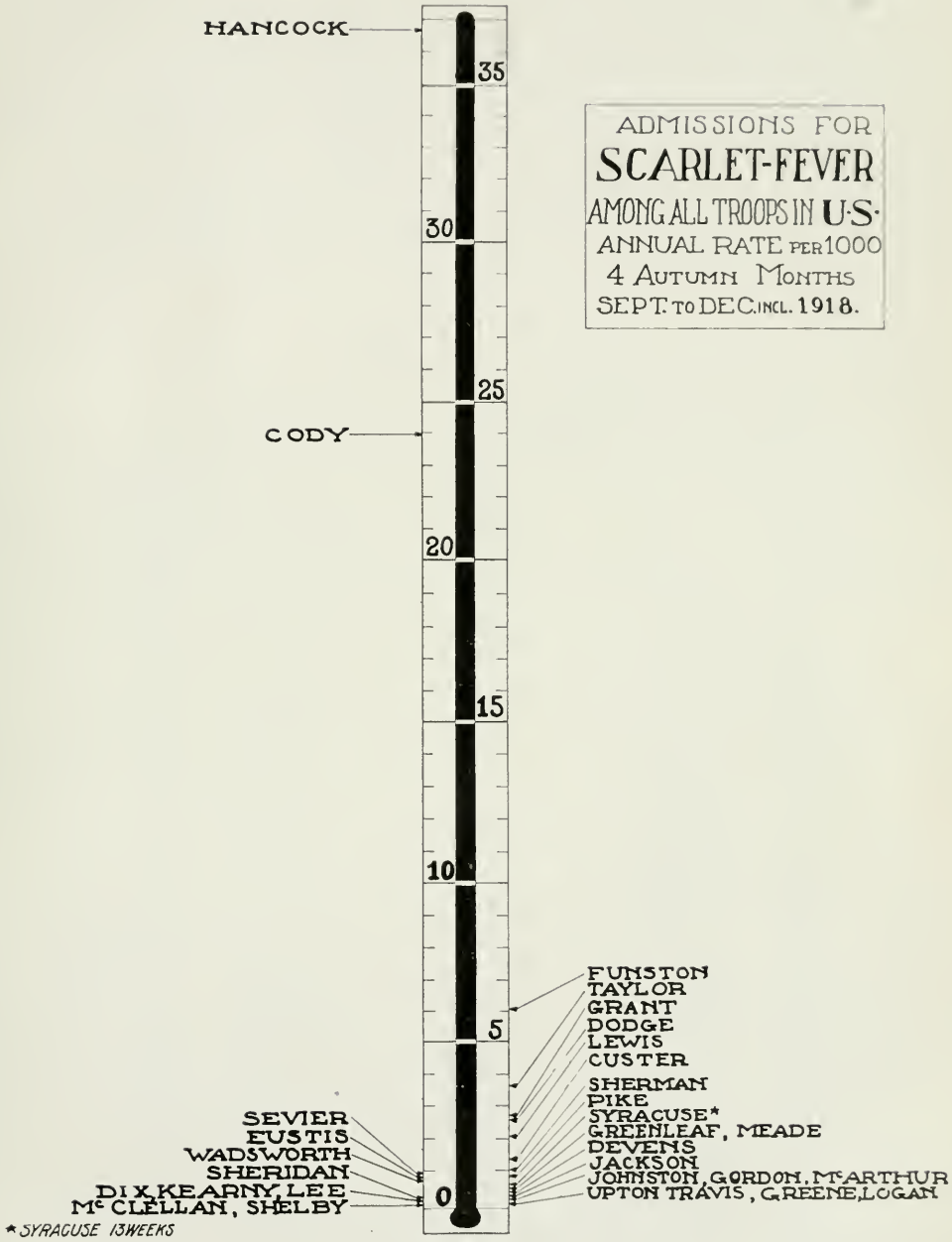
HANCOCK
CODY
35
30
25
20
15
10
5
0
ADMISSIONS FOR
SCARLET-FEVER
AMONG ALL TROOPS IN U.S.
ANNUAL RATE PER 1000
4 AUTUMN MONTHS
SEPT. TO DEC. INCL. 1918.
FUNSTON
TAYLOR
GRANT
DODGE
LEWIS
CUSTER
SHERMAN
PIKE
SYRACUSE*
GREENLEAF, MEADE
DEVENS
JACKSON
JOHNSTON, GORDON, MCARTHUR
UPTON TRAVIS, GREENE, LOGAN
SEVIER
EUSTIS
WADSWORTH
SHERIDAN
DIX, KEARNY, LEE
MC CLELLAN, SHELBY
*SYRACUSE 13 WEEKS

CHART XXIII.

cock and Cody, the former experiencing a rather severe epidemic in November. For the entire season there were 416 admissions for scarlet fever, but not a single death is reported from this cause. Of this total 212 occurred during the week ending November 15. Camp Cody had 48 admissions and stands second in the table with a rate of 24.8. The data for the autumn months are shown in Table 16, and illustrated in Chart XXIII. Cody's cases likewise occurred in the months of November and December. Thirty-one of the thirty-eight large camps had scarlet fever during the autumn season.

In commenting on the winter of 1917-18 it was stated that scarlet fever prevailed mostly in those camps which contained troops from the middle and far West. At this time the six camps with the highest rates were Pike, Lewis, Kearny, Sherman, Dodge and Grant. The same camps continued to have a relatively high scarlet fever rate, or at least higher than other camps, during the summer and during the fall. In the summer these camps were within the first fifteen in the table, Lewis, Dodge and Sherman standing at the top. In the autumn five of these camps are in the first twelve of the table, the

TABLE 17

MALARIA—FIVE SUMMER MONTHS

Week Ending April 5, 1918, to August 30, 1918

Annual Admission Rate per 1000 for All Troops in U. S.....4.1

ORDER	CAMP	AVERAGE STRENGTH IN THOUSANDS	NUMBER OF ADMISSIONS	ANNUAL ADMISSION RATE PER 1000
1	Beauregard	22.1	377	40.4
2	Shelby	20.5	214	24.6
3	Pike	36.5	363	23.5
4	Sevier	19.5	106	12.8
5	Travis	31.2	126	9.5
6	Johnston	17.6	69	9.3
7	Logan	15.1	56	8.8
8	Las Casas*	12.8	15	6.8
9	Greenleaf*	17.7	27	6.6
10	Sheridan	15.9	41	6.1
11	Gordon	36.4	84	5.5
12	Bowie	19.1	39	4.8
13	McClellan	18.5	36	4.6
14	Hancock	25.5	42	3.9
15	MacArthur*	15.5	18	3.6
16	Jackson	33.4	50	3.5
17	Wadsworth	21.7	28	3.5
18	Dix	46.1	57	2.9
19	Wheeler	23.8	28	2.8
20	Meade	36.3	38	2.5
21	Kearny	19.4	17	2.1
22	Fremont	19.9	16	1.9
23	Lee	42.5	25	1.4
24	Dodge	31.2	18	1.4
25	Lewis	34.2	19	1.3
26	Sherman	32.8	18	1.3
27	Grant	36.4	17	1.1
28	Devens	36.1	14	.9
29	Cody	24.5	6	.6
30	Upton	34.5	8	.5
31	Custer	20.5	6	.5
32	Funston	25.1	5	.5

*Las Casas—8 weeks—Week ending July 6 to Aug. 30.
*Greenleaf—12 weeks—Week ending June 14, to Aug. 30.
*MacArthur—17 weeks—Week ending May 10, to Aug. 30.

sixth, Kearny, dropping to twenty-fifth. The southern and eastern men were for the most part largely free from scarlet fever during the first winter season, and continued so for the rest of the year, the exception being Camp Hancock. That scarlet fever in the civil community, which furnishes men to the camp, is responsible for the continuation of the disease in the camp, is borne out by the continued prevalence of the disease in the middle west and far western camps. In addition to the six we have mentioned as having high rates during the winter, we may add Custer, Logan and Funston, which were in the first eight of the table in the summer months, Custer and Funston being likewise in the first eight of the autumn table. In the latter period, Logan had but one case.

The deaths from scarlet fever have been few, but four being reported in all the large camps during the summer, and but five during the autumn.

TABLE 18

MALARIA—FOUR AUTUMN MONTHS

Week Ending September 6, 1918, to December 27, 1918

Annual Admission Rate per 1000 for All Troops in U. S.....2.7

ORDER	CAMP	AVERAGE STRENGTH IN THOUSANDS	NUMBER OF ADMISSIONS	ANNUAL ADMISSION RATE PER 1000
1	Beauregard	13.7	192	42.8
2	Las Casas	12.8	131	31.3
3	Wheeler	12.5	66	16.1
4	Sevier	23.3	92	12.1
5	Eustis	14.0	49	10.7
6	Logan	14.3	43	9.0
7	Shelby	12.1	33	8.2
8	Johnston	19.7	53	8.1
9	Gordon	29.3	73	7.5
10	Bowie	9.8	19	5.8
11	Pike	44.2	58	3.9
12	McClellan	24.6	31	3.8
13	Jackson	38.2	29	2.3
14	Kearny	17.5	11	1.9
15	Travis	32.3	18	1.7
16	Wadsworth	15.3	8	1.6
17	MacArthur	20.7	9	1.3
18	Lewis	35.3	15	1.3
19	Humphreys	24.1	10	1.2
20	Greenleaf	19.9	7	1.1
21	Hancock	34.0	13	1.1
22	Funston	49.0	14	.9
23	Dodge	28.5	6	.6
24	Cody	5.9	1	.5
25	Sheridan	22.0	4	.5
26	Sherman	30.9	4	.4
27	Meade	42.1	5	.4
28	Lee	43.8	6	.4
29	Grant	35.0	5	.4
30	Dix	35.0	4	.3
31	Devens	39.5	4	.3
32	Greene	16.6	1	.2
33	Fremont	12.9	1	.2

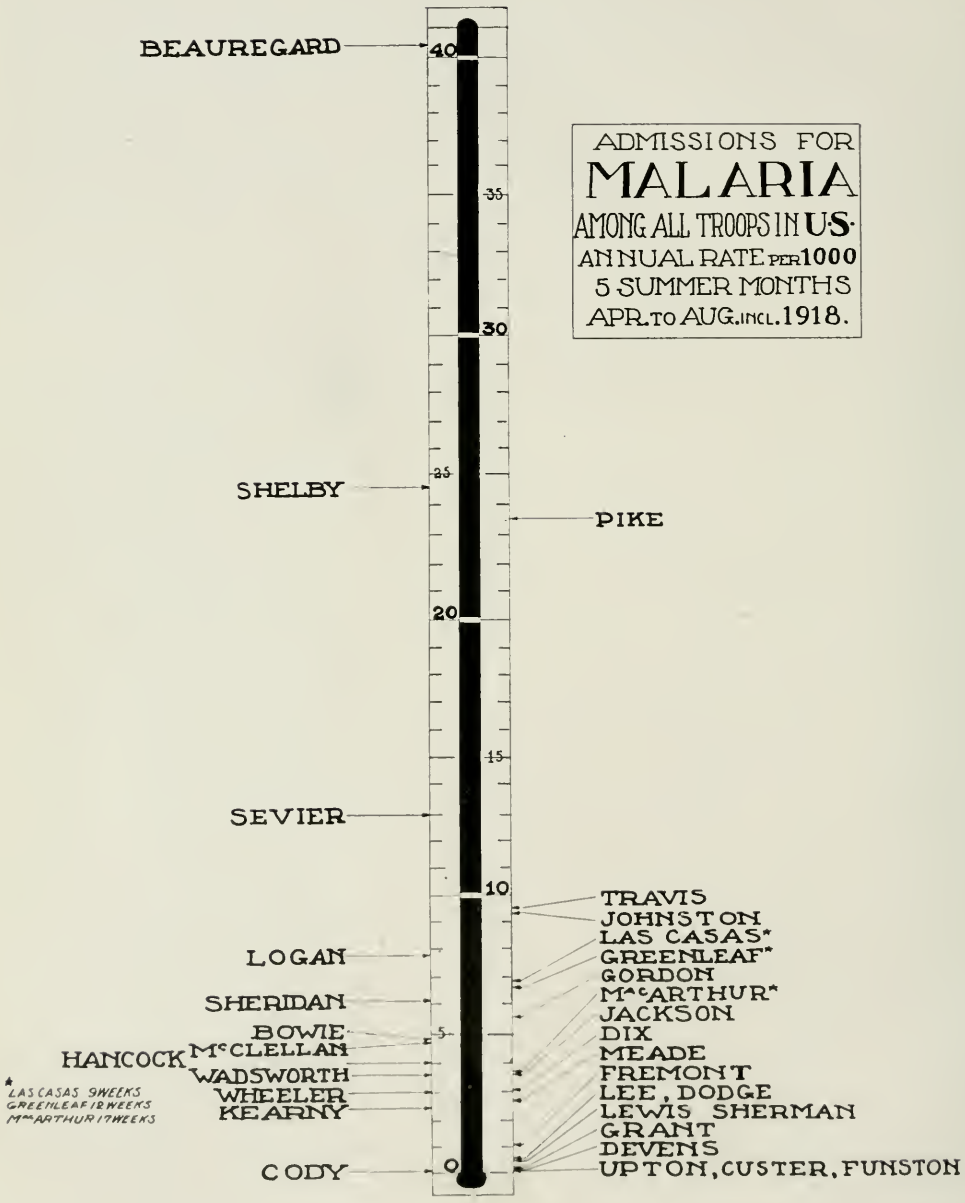
ADMISSIONS FOR
MALARIA
AMONG ALL TROOPS IN U.S.
ANNUAL RATE PER 1000
5 SUMMER MONTHS
APR. TO AUG. INCL. 1918.
40
35
30
25
20
15
10
5
0
BEAUREGARD
SHELBY
PIKE
SEVIER
LOGAN
SHERIDAN
BOWIE
HANCOCK
McCLELLAN
WADSWORTH
WHEELER
KEARNY
CODY
TRAVIS
JOHNSTON
LAS CASAS*
GREENLEAF*
GORDON
McARTHUR*
JACKSON
DIX
MEADE
FREMONT
LEE, DODGE
LEWIS SHERMAN
GRANT
DEVENS
UPTON, CUSTER, FUNSTON
* LAS CASAS 9 WEEKS
GREENLEAF 12 WEEKS
McARTHUR 17 WEEKS

CHART XXIV.

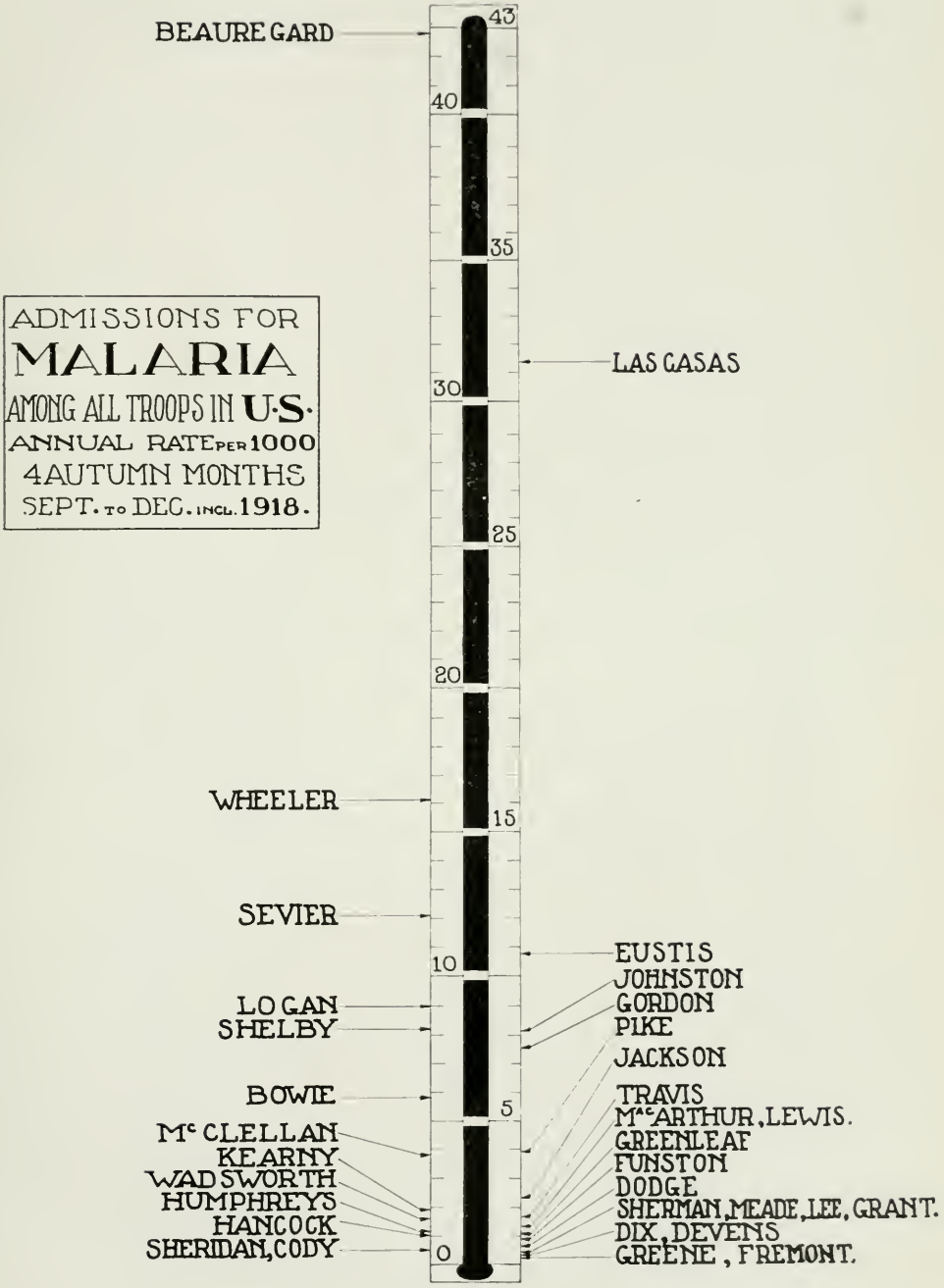
ADMISSIONS FOR
MALARIA
AMONG ALL TROOPS IN U.S.
ANNUAL RATE PER 1000
4 AUTUMN MONTHS
SEPT. TO DEC. INCL. 1918.
45
40
35
30
25
20
15
10
5
0
BEAUREGARD
LAS CASAS
WHEELER
SEVIER
LOGAN
SHELBY
BOWIE
Mc CLELLAN
KEARNY
WADSWORTH
HUMPHREYS
HANCOCK
SHERIDAN, CODY
EUSTIS
JOHNSTON
GORDON
PIKE
JACKSON
TRAVIS
Mc ARTHUR, LEWIS.
GREENLEAF
FUNSTON
DODGE
SHERMAN, MEADE, LEE, GRANT.
DIX, DEVENS
GREENE, FREMONT.

CHART XXV.

E. MALARIA

Malaria was most prevalent during the summer of 1918, the camps of southern men showing the greatest amount. Malaria data are given in Table 17, and illustrated in Chart XXIV. Beauregard stands at the top of the list with an annual admission rate of 40.4. This is followed by Shelby with a rate of 24.6, and Pike with 23.5. The remaining twenty-nine camps have rates varying from 12.8 to 5.8.

As seen in Table 18, the data of which are illustrated in Chart XXV, malaria during the autumn was likewise greatest at Beauregard whose rate was slightly greater than during the summer. The five camps with rates above ten are, in addition to Beauregard, Las Casas with a rate of 31.3, Wheeler with 16.1, Sherman, 12.1 and Eustis, 10.7. It is again the camps of southern troops where malaria is most prevalent.

The eradication of malaria is primarily a matter of sanitation, that of wiping out the breeding places of the malarial mosquito, but, the presence of malaria in army camps is not a criterion of the way this mosquito elimination work has been carried out. The malaria reports have come from men who contracted malaria prior to their entrance into the army. There is little if any evidence that malaria has spread among uninfected individuals in the camps.

Of 9 cases of malaria at Fremont from June 1 to August 31, all gave a history of previous attack before arrival at camp.

Devens reports that with one exception during the summer of 1918, all of the few cases of malaria were men from the southern states who brought the disease with them.

Sevier informs us that "no cases of malaria have developed—except in men coming from places where malaria is present." This refers to the summer months of June, July and August.

From Meade we learn that "of the 24 discovered cases of malaria in July (both latent and febrile cases) all occurred in recent arrivals and were plainly recurrences of old infections."

TABLE 19

TUBERCULOSIS—FIVE SUMMER MONTHS

Week Ending April 5, 1918, to August 30, 1918

Annual Death Rate per 1000 for All Troops in U. S.....18.

ORDER	CAMP	AVERAGE STRENGTH IN THOUSANDS	NUMBER OF DEATHS	ANNUAL DEATH RATE PER 100,000
1	Gordon	36.4	5	32.
2	Lee	42.5	5	28.
3	Upton	34.5	4	28.
4	Meade	36.3	4	26.
5	Pike	36.5	4	26.
6	Dodge	31.2	3	23.
7	Sherman	32.8	3	22.
8	Taylor	34.7	3	20.
9	Grant	36.4	3	20.
10	Logan	15.1	1	16.
11	Travis	31.2	2	15.
12	Sheridan	15.9	1	15.
13	Jackson	33.4	2	14.
14	Kearny	19.4	1	12.
15	Fremont	19.9	1	12.
16	Dix	46.1	2	10.
17	Funston	25.1	1	9.
18	Hancock	25.5	1	9.
19	Lewis	34.2	1	7.

F. TUBERCULOSIS

Cases of tuberculosis are not reported weekly by telegraph to the Surgeon General's office, and we have therefore, but a record of the deaths from this cause. There have been relatively few deaths from tuberculosis as compared with certain other diseases. However, inasmuch as the American soldier is supposed to pass a rigid physical examination before entering the army, we may regard the death rate from this cause as unnecessarily high. During the winter of 1917-18 the highest rates are found at Wheeler, Pike, Beauregard, Wadsworth and Sherman, these camps being represented by personnel from the south and east. Tuberculosis deaths were less during the summer.

TABLE 20

TUBERCULOSIS—FOUR AUTUMN MONTHS

Week Ending September 6, 1918, to December 27, 1918

Annual Death Rate per 1000 for All Troops in U. S.....46.

ORDER	CAMP	AVERAGE STRENGTH IN THOUSANDS	NUMBER OF DEATHS	ANNUAL DEATH RATE PER 100,000
1	Humphreys	24.1	5	64.
2	Gordon	29.3	5	52.
3	Meade	42.1	7	51.
4	Jackson	38.2	6	48.
5	Beauregard	13.7	2	45.
6	Taylor	54.9	7	39.
7	Funston	49.0	6	38.
8	Hancock	34.0	4	36.
9	Grant	35.0	4	35.
10	Travis	32.3	3	28.
11	Wheeler	12.5	1	25.
12	Upton	27.9	2	22.
13	Lee	43.8	3	21.
14	Sherman	30.9	2	20.
15	Dix	35.0	2	18.
16	Custer	36.1	2	17.
17	Johnston	19.7	1	16.
18	Greenleaf*	19.9	1	15.
19	Sheridan	22.0	1	14.
20	Pike	44.2	2	14.
21	Sevier	23.3	1	13.
22	Lewis	35.3	1	9.
23	Devens	39.5	1	8.

*Greenleaf—12 weeks—Week ending June 14, to Aug. 30.

Nineteen camps reported deaths. In the autumn twenty-three camps reported deaths, the rates during the season running up to 64. Of the camps which stood among the first five in the winter table, none are represented in the first five of the summer table, or in the autumn table. Two camps which stood high during the summer, namely, Meade and Gordon, were likewise within the first five during the autumn. The number of deaths was not over seven per camp during either season. (See Tables 19, 20.)

G. DIPHTHERIA

During the winter season, deaths from diphtheria were reported in seven out of twenty-nine large camps. In the summer but six camps reported deaths, and in the autumn but one. At no camp during the summer and fall was more than one diphtheria death registered. (See Table 21.)

From Aug. 25, 1917, to May 31, 1918, there were 62 cases of diphtheria with three deaths at Cody. This is about one-fourth the measles incidence. Of 3500 cultures taken among men as they arrived in the recruit camp, 27 carriers were found. This is .77 per cent. In most of the regiments about one per cent of the strength were carriers. Few carriers gave a previous history of the disease. Chronic carriers frequently gave history of sore throat and those with hypertrophied tonsils cleared up after the tonsils were removed. It was the custom to isolate and treat carriers four times daily with dichloramine-T solution.

From June 1 to Aug. 31, there were nine diphtheria cases without fatality at Cody. The incidence during the winter was about 7 per month and for the summer 3 per month.

TABLE 21

DIPHTHERIA—FIVE SUMMER MONTHS

Week Ending April 5, 1918, to August 30, 1918

Annual Death Rate per 1000 for All Troops in U. S..... .84

ORDER	CAMP	AVERAGE STRENGTH IN THOUSANDS	NUMBER OF DEATHS	ANNUAL DEATH RATE PER 100,000
1	Dodge	31.2	1	7.
2	Sherman	32.8	1	7.
3	Jackson	33.4	1	7.
4	Lewis	34.2	1	7.
5	Meade	36.3	1	7.
6	Dix	46.1	1	5.

FOUR AUTUMN MONTHS

Week Ending September 6, 1918, to December 27, 1918

Annual Death Rate per 1000 for All Troops in U. S.....1.0

1	McClellan	24.6	1	12.

Dodge and Grant each reported 7 cases of diphtheria and no deaths from June 1 to Sept. 1. Sherman had 21 cases and no deaths in the same time and Fremont 4 cases. One of these was contracted in the base hospital, the patient being readmitted with this diagnosis following one day's release from a 25-day detention in the hospital. Six carriers were found in the ward first occupied by the patient. There was but one case of diphtheria, non-fatal, at Meade during July and August.

Our record of cases of diphtheria is incomplete as no weekly report is made. We may say that diphtheria has been a disease of minor consequence in the American Army.

II. TYPHOID FEVER

As has already been pointed out in the tables for the army as a whole, typhoid fever and its associated diseases, the paratyphoids, have been very infrequent during the summer and autumn seasons of 1918. (See Tables 22 and 23.) Admissions have varied from one to nineteen, the latter number being reported from Camp Lee during the summer. The admission rate for Lee, however, was not over 1.1 per 1000, whereas during the previous winter the rates of Dix and Bowie were 2.1 and 4.1, respectively. Typhoid was reported at twenty-four of the large camps during the summer, and at twenty-three during the autumn. As a rule it has been the southern camps rather than the northern and western which have reported the most typhoid. In the autumn Logan stands at the top of the table with an admission of 1.3. Forrest has the same rate, but this merely represents four cases during four months.

Sherman reports a colored soldier arriving in camp June 20 who was taken ill the next day and admitted to the hospital with typhoid fever. He had not received the typhoid vaccination. Another colored soldier arriving in camp June 19, was admitted to the base hospital June 25, diagnosis undetermined. On July 1 the case was pronounced typhoid. This man had received his first typhoid prophylactic.

Two cases of typhoid and one of paratyphoid occurred at Meade in August among recruits from the rural districts of Kentucky. The two typhoid cases had received the first immunizing dose of triple typhoid vaccination in July. The second dose was given at Meade on July 27. In one of these cases the third dose was given a few days before admission to the hospital. The paratyphoid case had received the typhoid vaccination in June, 1917, and paratyphoid in July, 1917.

TABLE 22

TYPHOID AND PARATYPHOID—FIVE SUMMER MONTHS

Week Ending April 5, 1918, to August 30, 1918

Annual Admission Rate per 1000 for All Troops in U. S.....0.26

ORDER	CAMP	AVERAGE STRENGTH IN THOUSANDS	NUMBER OF ADMISSIONS	ANNUAL ADMISSION RATE PER 1000	NUMBER OF DEATHS
1	Greene*	7.5	1	1.7	0
2	Sevier	19.5	10	1.2	0
3	Lee	42.5	19	1.1	2
4	Sheridan	15.9	6	.9	0
5	Shelby	20.5	7	.8	1
6	Jackson	33.4	11	.8	3
7	Wadsworth	21.7	6	.7	1
8	Johnston	17.6	4	.5	1
9	Gordon	36.4	7	.5	2
10	Travis	31.2	5	.4	1
11	Bowie	19.1	3	.4	1
12	Sherman	32.8	4	.3	1
13	Devens	36.1	4	.3	0
14	Beauregard	22.1	2	.2	0
15	Cody	24.5	2	.2	0
16	Logan	15.1	1	.2	0
17	Pike	36.5	2	.1	2
18	Fremont	19.9	1	.1	0
19	Hancock	25.5	1	.1	0
20	Funston	25.1	1	.1	0
21	Custer	26.5	1	.08	0
22	Upton	34.5	1	.07	0
23	Lewis	34.2	1	.06	0
24	Meade	36.3	1	.06	0

*Greene—3 weeks—Week ending Aug. 16, to Aug. 30.

Three cases of typhoid reported from Devens were admitted to the hospital almost directly from civilian life.

Custer reports the case of a soldier who was inducted into the service on August 26 prior to which date he had been at home where a sister was ill of typhoid. This man received his first inoculation August 28 and his second September 4. He was admitted to the base hospital with typhoid on September 10.

Typhoid carriers are not numerous if we may judge by the reports from Fremont. Cooks and food handlers to the number of 1,037 were examined by cultures from stools and urine during May and June. But one carrier was found and he gave no previous history of typhoid. His typhoid prophylaxis had been completed the year previous.

Table 23

Typhoid and Paratyphoid—Four Autumn Months

Week Ending September 6, 1918, to December 27, 1918

Annual Admission Rate per 1000 for All Troops in U. S.....0.27

ORDER	CAMP	AVERAGE STRENGTH IN THOUSANDS	NUMBER OF ADMISSIONS	ANNUAL ADMISSION RATE PER 1000	NUMBER OF DEATHS
1	Logan	14.3	6	1.3	0
2	Forrest	9.2	4	1.3	0
3	Pike	44.2	12	.8	1
4	Fremont	12.9	3	.7	0
5	Gordon	29.3	7	.7	2
6	Funston	49.0	1	.6	3
7	Cody	5.9	1	.5	0
8	Sheridan	22.0	4	.5	0
9	Wheeler	12.5	2	.5	1
10	Lee	43.8	7	.5	1
11	Meade	42.1	5	.4	1
12	MacArthur*	20.7	3	.4	0
13	Beauregard	13.7	2	.4	0
14	Greene*	16.6	2	.4	0
15	Greenleaf*	19.9	1	.2	0
16	McClellan	24.6	2	.2	0
17	Shelby	12.1	1	.2	2
18	Wadsworth	15.3	1	.2	0
19	Custer	36.1	3	.2	2
20	Devens	39.5	2	.2	0
21	Sherman	30.9	1	.1	0
22	Travis	32.3	3	.1	1
23	Upton	27.9	1	.1	0

*MacArthur—17 weeks—Week ending May 10, to Aug 30.
*Greene—3 weeks—Week ending Aug. 16, to Aug. 30.
*Greenleaf—12 weeks—Week ending June 14, to Aug. 30.

It is true that the death rate from this cause for the army as a whole increased from winter to autumn, but in view of the few cases involved there is little significance attached to this.

I. VENEREAL DISEASES

The highest admission rates for the venereal diseases were during the summer; 820 per 1000 at Syracuse, and 736 at Greene. As the period of time covered by these rates is not over three weeks, we may look upon the rate of 546 at Wadsworth as the highest. This rate is higher than that at Pike, which headed the table the previous winter season, with a rate of 312. Pertinent data are shown in Tables 24 and 25 for the summer and autumn seasons. The five camps which stood the highest in the winter of 1917-18 were Pike, Jackson, Lee, Travis, and Logan. During the summer months the five highest camps were Wadsworth, Jackson, Custer, Upton and Sheridan; and during the autumn, Bowie, Dix, Pike, Syracuse and Wadsworth. There is little significance to be attached to these figures without knowing the personnel and the recruit arrivals. As shown in the last column of the autumn table a very great majority of venereal cases existed prior to entering the army. The figures showing "per cent of new cases" must be regarded as indicatory, however, rather than absolute, for the method of reporting venereal diseases has not been worked out in a wholly satisfactory manner, and for that reason some camps have reported with much greater accuracy and thoroughness than others, and it is these camps which as a consequence may have the highest percentage of new to total cases.

TABLE 24

VENEREAL DISEASES—FIVE SUMMER MONTHS

Week Ending April 5, 1918, to August 30, 1918

Annual Admission Rate per 1000 for All Troops in U. S.....156.

ORDER	CAMP	AVERAGE STRENGTH IN THOUSANDS	NUMBER OF ADMISSIONS	ANNUAL ADMISSION RATE PER 1000
1	Syracuse*	13.5	426	820.
2	Greene*	7.5	319	736.
3	Wadsworth	21.7	5028	546.
4	Jackson	33.4	6359	449.
5	Custer	26.5	3662	326.
6	Upton	34.5	4668	319.
7	Sheridan	15.9	2042	303.
8	Lewis	34.2	4137	286.
9	MacArthur*	15.5	1415	279.
10	Gordon	36.4	4011	260.
11	Lee	42.5	4140	229.
12	Funston	25.1	2384	225.
13	Dodge	31.2	2412	182.
14	Sherman	32.8	2438	175.
15	Logan	15.1	975	152.
16	Beauregard	22.1	1356	145.
17	Sevier	19.5	1145	139.
18	Meade	36.3	2017	132.
19	Devens	36.1	1891	124.
20	Johnston	17.6	924	123.
21	Hancock	25.5	1314	122.
22	Travis	31.2	1570	119.
23	McClellan	18.5	899	115.
24	Bowie	19.1	908	112.
25	Dix	46.1	2073	106.
26	Pike	36.5	1568	101.
27	Taylor	24.7	1350	92.
28	Wheeler	23.8	853	84.6
29	Las Casas*	12.8	187	84.5
30	Greenleaf*	17.7	310	76.0
31	Shelby	20.5	611	70.4
32	Cody	24.5	685	66.0
33	Kearny	19.4	465	56.6
34	Fremont	19.9	470	55.7
35	Grant	36.4	672	43.6

*Syracuse—2 weeks—Week ending Aug. 23 to Aug. 30.
*Greene—3 weeks—Week ending Aug. 16 to Aug. 30.
*MacArthur—17 weeks—Week ending May 10, to Aug. 30.
*Las Casas—9 weeks—Week ending July 5 to Aug. 30.
*Greenleaf—12 weeks—Week ending June 14 to Aug. 30.

The figures are given for what they are worth and the best we can say is that as a rule less than 10 per cent of venereal disease is contracted by men after entering the army.

J. MUMPS

The prevalence of mumps among the troops in this country must be judged from the reports of a limited number of camps. This disease is not included in the weekly telegraphic report and it is only the records sent in from the camps voluntarily that are available.

The incidence of mumps was not unlike measles numerically. During the summer months of June, July and August, 1918, reports from eight large camps show 2291 cases

TABLE 25

VENEREAL DISEASE—FOUR AUTUMN MONTHS

Week Ending September 6, 1918, to December 27, 1918

Annual Admission Rate per 1000 for All Troops in U. S.....132.

ORDER	CAMP	AVERAGE STRENGTH IN THOUSANDS	NUMBER OF ADMISSIONS	ANNUAL ADMISSION RATE PER 1000	NUMBER OF CASES CONTRACTED SINCE ENLISTMENT	PER CENT NEW TO TOTAL CASES
1	Bowie	9.8	3497	1090.	53	1.5
2	Dix	35.0	10602	927.	12	.1
3	Pike	44.2	8891	616.	45	.5
4	Syracuse*	7.4	729	301.	0	0.
5	Wadsworth	15.3	1548	310.	57	3.6
6	Greene	16.6	1620	299.	45	2.7
7	Dodge	28.5	2680	288.	125	4.6
8	Beauregard	13.7	1166	260.	58	4.9
9	Upton	27.9	1603	176.	41	2.5
10	Johnston	19.7	1094	170.	427	39.
11	Jackson	38.2	1931	155.	9	.5
12	Meade	42.1	2105	153.	85	4.
13	Logan	14.3	704	151.	65	9.2
14	Shelby	12.1	554	140.	144	26.
15	Forrest	9.2	413	137.	10	2.4
16	Gordon	29.3	1160	121.	16	1.3
17	Eustis	14.0	507	111.	10	1.9
18	Lewis	35.3	1247	108.	85	6.8
19	Funston	49.0	1658	104.	9	.5
20	Hancock	34.0	1083	97.4	143	13.
21	Kearny	17.5	495	86.5	145	29.
22	Wheeler	12.5	342	83.7	15	4.3
23	Travis	32.3	871	82.5	55	6.3
24	Sheridan	22.0	519	72.2	59	11.
25	Custer	36.1	831	70.4	98	12.
26	Lee	43.8	909	63.5	58	6.3
27	Sevier	23.3	469	61.6	83	18.
28	Humphreys	24.1	482	61.2	46	9.5
29	Sherman	30.9	608	60.2	75	12.
30	McClellan	24.6	463	57.5	15	3.2
31	Cody	5.9	109	56.5	0	0.
32	Devens	39.5	647	50.1	170	26.
33	Greenleaf	19.9	284	43.6	3	1.0
34	Taylor	54.9	868	48.3	78	8.9
35	Fremont	12.9	178	42.2	42	24.
36	MacArthur	20.7	279	41.2	71	25.
37	Grant	35.0	468	40.6	0	0.
38	Las Casas	12.8	111	26.5	0	0.

*Syracuse—13 weeks—Week ending Sept. 6, to Nov. 29

of mumps to 1699 cases of measles. (See Table 26.) There was 35 per cent more mumps than measles. The excess of mumps over measles was somewhat less during the previous winter period, when there were reported from nine camps 14,717 cases of mumps and 11,816 cases of measles, mumps being 25 per cent greater.

TABLE 26

WINTER AND SPRING 1917-18

CAMP	PERIOD	NO. WEEKS	MEASLES	MUMPS
Devens	10/1/17-7/31/18	43	785	778
Taylor	10/3/17-12/31/17	13	903	114
Cody	8/25/17-5/31/18	39	235	104
Kearny	10/7/17-5/3/18	37	1538	1674
Lee	10/1/17-4/30/18	30	1143	3363
Beauregard	9/1/17-5/3/18	38	2627	3569
Johnston	12/24/17-4/30/17	18	447	591
Sevier	8/28/17-4/30/18	35	3576	3217
McClellan	10/1/17-4/30/18	30	542	307
Total			11816	14717

SUMMER 1918

Dodge	June 1-Aug. 31	13	525	369
Cody	"	13	141	119
Sherman	"	13	82	116
Grant	"	13	141	348
Gordon	"	13	312	936
Fremont	"	13	94	92
Sevier	"	13	344	278
Meade	July 1 to Aug. 31	9	60	33
Total			1699	2291

The Annual Report of the Surgeon General for the entire year 1917 gives 47,573 measles admissions to 21,725 for mumps. After Jan. 1, mumps appeared in greater numbers than measles.

As between the cold and warm weather periods (and it must be remembered in this connection that the cold weather is coincident with the earliest days of the men in camp whereas the warm period covers the termination of the training) mumps was more frequent in the former. Expressed as an annual rate per 1000 the rates for the winter and spring period were as follows:

The summer rates were:

Beauregard	252.	Gordon	94.6
Sevier	182.	Sevier	73.6
Lee	182.	Dodge	41.7
Kearny	112.	Grant	37.5
Devens	31.2	Cody	19.7
McClellan	21.9	Fremont	16.1
Taylor	17.5	Sherman	14.1
Cody	6.3	Meade	5.1

Mumps was more prevalent among the southern than northern troops in the winter. The climatic influence during the summer can not be judged owing to the paucity of the data.

During the month of May recruits of the April draft located in the Depot Brigade at Camp Grant contributed nearly all of the 149 cases of mumps occurring in that month. Mumps was most common among the negro troops from June 1 to Aug. 31. It assumed epidemic proportions in June following the arrival of negro recruits from the southern states. Cases again increased in number after the arrival of another lot of colored recruits on July 30. Some cases developed among men who had been in camp less than 48 hours. The cases were sporadic among white troops.

From Sept. 1 to Oct. 1, 1918, there were 238 cases at Grant, 90 per cent of which were among colored men of the development and labor battalions. Only 5 per cent of these cases were among new recruits.

During 1917 there were but eight deaths among 21,725 cases in the army in this country. The greatest objection to mumps is that it makes soldiers noneffective, constituting a burden to the base hospital. In 1917 this disease kept men in the hospital 11.7 days as compared to 11.3 days for measles. During the winter season at Kearny mumps caused 11.7 per cent of all admissions to the hospital and quarters. The average time for each case in the hospital was 12 days.

Capt. Burns, epidemiologist at Camp Lewis believes that greater caution should be used in handling mumps. He says "the men are sick. They are taken to the one place in camp where other contagious diseases are cared for. They tax the service and are often exposed to cross infection. The men are weak for a considerable time after being discharged to duty." A serious phase of the question is sounded by Capt. Burns when he reports that "33 per cent of the cases of mumps admitted to the base hospital in 1918 were complicated by orchitis." This complication was far more frequent at Lewis than at other camps of which we have record. Devens reports that complications were few and that no disability followed the disease. Orchitis is reported as rare at Cody.

At Kearny mumps has differed from measles and in fact from most other diseases in its relatively belated appearance in camp. Thus at Kearny during the period Sept. 7, 1917, to May 31, 1918, only 10 per cent of 1674 cases occurred prior to Jan. 1. During the same period 88 per cent of measles had occurred, 65 per cent of bronchitis, 38 per cent of tonsillitis, 33 per cent of diphtheria, 21 per cent scarlet fever, 74 per cent epidemic cerebrospinal meningitis, 75 per cent lobar pneumonia, and 71 per cent of bronchial pneumonia. The distribution of 1674 cases of mumps by months was as follows:

		PER CENT OF TOTAL NUMBER
(1917)	Sept.	.4
	Oct.	.6
	Nov.	3.5
	Dec.	6.2
(1918)	Jan.	13.6
	Feb.	30.8
	Mar.	45.8

The same experience is reported from Cody where the cases by months were:

		NUMBER OF CASES
(1917)	Aug.	1
	Sept.	1
	Oct.	2
	Nov.	2
	Dec.	3
(1918)	Jan.	7
	Feb.	12
	Mar.	25
	Apr.	20
	May	31

While the disease was frequently introduced by draft increments it was by no means confined to men just entering camp, as is shown by the following analysis at Cody:

LENGTH OF SERVICE	NO. OF CASES
1 month or less	30
1 to 2 months	40
2 to 3 months	27
Over 3 months	22

K. OTHER DISEASES

Most prominent among diseases which have not been touched upon, exclusive of pneumonia, were the minor respiratory affections variously labeled *bronchitis, tonsillitis* and *influenza*. The exact number of these we shall never know, for many escaped record. The number given as having been admitted to the hospital is but a partial record.

From June 1 to Aug. 31, Sherman admitted 202 cases of tonsillitis and 16 of influenza, the latter having no laboratory confirmation. Fremont at this time reported 18 cases of *Vincent's Angina*. Gordon informs us that "colds, bronchitis, sore throat, and kindred affections have been prevalent in this command—and has predisposed to the graver respiratory diseases."

The most annoying feature of these minor infections is the complication likely to develop. Epidemiologists who have studied the matter closely have observed that not infrequently pneumonia is preceded by some form of cold. Thus at Camp Dodge during the summer season an investigation of 33 pneumonia cases proved that 25 were preceded by either colds, la grippe, bronchitis or influenza. Major Woolley of Devens reports that in a very large majority of the pneumonia cases during the summer season the onset was not sharp, but was preceded by a complaint of coughs, colds, etc. He believes that patients with acute infections of the upper respiratory tract should be regarded as possible future subjects of pneumonia. We believe this to be generally true in spite of the fact that the Surgeon General's Report for 1917 gives among 10,668 cases of pneumonia but 20 following bronchitis, 19 following influenza, 7 following tonsillitis and 2 following laryngitis. Many of the so-called primary pneumonias follow in the wake of a debilatory cold of which there is no record.

The evidence of Fremont on the west coast is contrary to the above, for during June, July, and August, 1918, the majority of 51 cases of lobar pneumonia gave no previous history of bad colds, bronchitis or tonsillitis.

The autumn season of 1918 witnessed an increasing number of minor respiratory affections before the advent of influenza.

German Measles has been common in many camps, but the statistical data are unreliable owing to confusion with measles. Cody reports that great care was exercised in differentiating the two measles and from Aug. 25, 1917, to May 31, 1918, 1315 cases of German measles were reported and but 235 measles.

In the entire year, 1917, there were but 8,982 German measles cases among the troops in this country as against 47,573 measles.

In the summer months of June, July and August, Cody reported but 2 German measles to 141 measles. Curiously enough, these identical figures represent the situation at Grant during the summer. Fremont reported 14 German measles and 94 measles, Sevier 7 German measles and 344 measles. If we may rely upon the diagnosis, German measles was much less common during the warm months than during the winter.

Chicken pox was infrequent. In 1917, this disease amounted to but 0.6 per cent of measles. During June, July and August Gordon reported one case, Fremont 4 cases and Grant 2 cases.

Whooping cough was likewise almost unknown. But 25 cases occurred in 1917 and none to our knowledge in 1918.

Smallpox was more prevalent than chicken pox, judged by the few reports available for the warm period of the summer season. Cody had one case, a recruit from Oklahoma who entered the hospital four days after his arrival in camp. Dodge reported eight cases

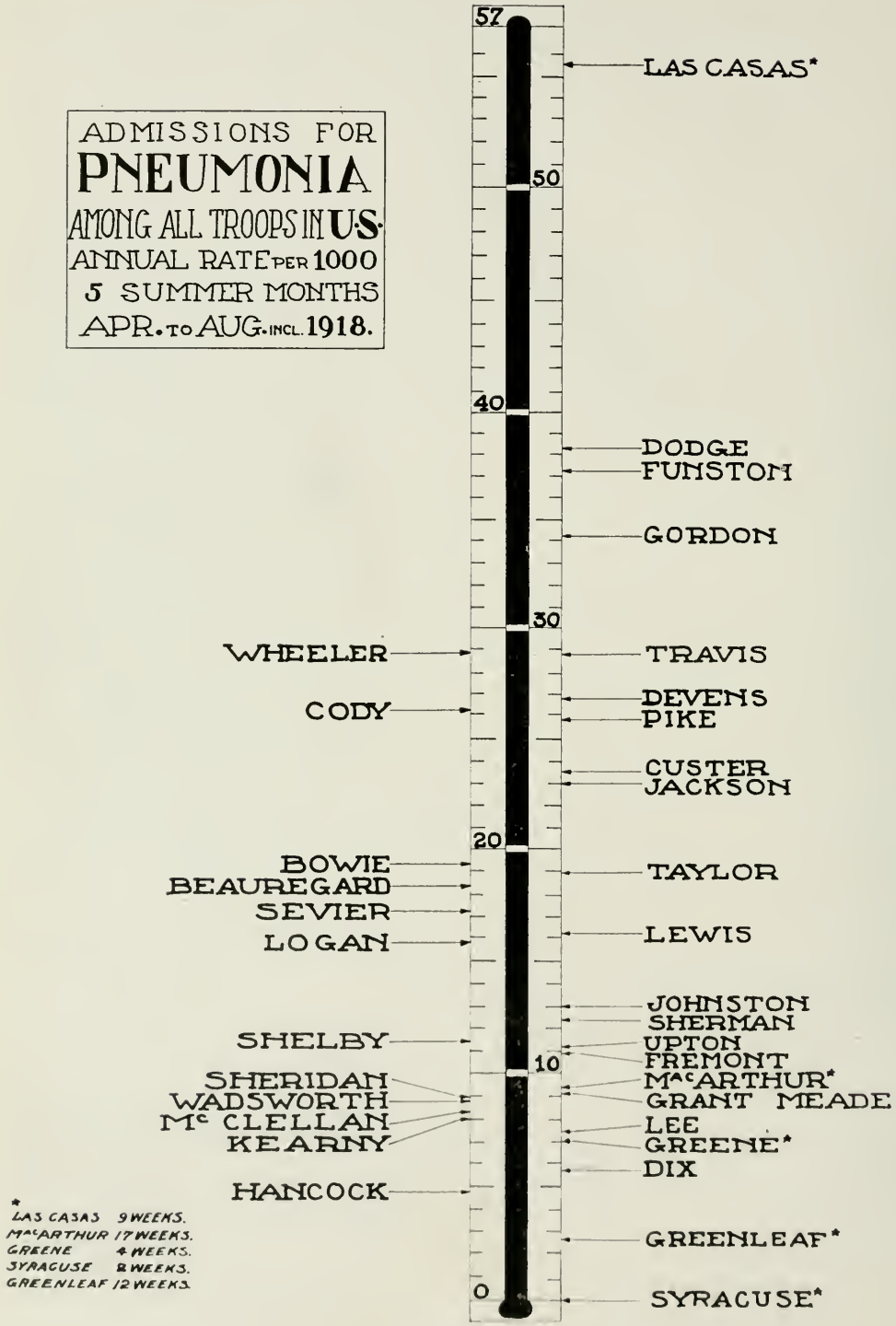
ADMISSIONS FOR
PNEUMONIA
AMONG ALL TROOPS IN U.S.
ANNUAL RATE PER 1000
5 SUMMER MONTHS
APR. TO AUG. INCL. 1918.
57
50
40
30
20
10
0
LAS CASAS*
DODGE
FUNSTON
GORDON
TRAVIS
DEVENS
PIKE
CUSTER
JACKSON
TAYLOR
LEWIS
JOHNSTON
SHERMAN
UPTON
FREMONT
MacARTHUR*
GRANT
MEADE
LEE
GREENE*
DIX
GREENLEAF*
SYRACUSE*
WHEELER
CODY
BOWIE
BEAUREGARD
SEVIER
LOGAN
SHELBY
SHERIDAN
WADSWORTH
Mc CLELLAN
KEARNY
HANCOCK
* LAS CASAS 9 WEEKS.
MacARTHUR 17 WEEKS.
GREENE 4 WEEKS.
SYRACUSE 2 WEEKS.
GREENLEAF 12 WEEKS.

CHART XXVI.

from June 1 to Aug. 31. Two of these cases were drafted men arriving in camp in the eruptive stage. Grant had two cases, Sevier nine.

Fremont reported one case of *anthrax* during the summer. Two cases of localized anthrax occurred at Camp Lewis during June and July which were diagnosed both clinically and bacteriologically. These cases occurred at the time the 91st Division left camp. En route to Hoboken 11 more cases were discovered and transferred to the Base Hospital at Camp Merritt. These cases were mild in type, "the lesion being located upon the shaven area of the neck." There are other instances known where anthrax was proved to have been transmitted by infected shaving brushes.

Bacillary dysentery, to the number of 12 cases with two deaths was reported from Meade during July and August. This was coincident with a sharp rise in gastrointestinal disorders and diarrhœs about the middle of August and due to a temporary breakdown in the chlorination of the water. As will be seen in Chart X dysentery of an unstated form was more prevalent in the army at large in the latter half of 1918 than in the first part. The annual rate exceeded one per 1000 on only seven occasions during 1918. Dysentery, so called, was more prevalent than typhoid.

L. PNEUMONIA DURING SUMMER SEASON

It has been thought best to separate the autumn from the summer season in discussing the pneumonia situation. This is owing to the close association between pneumonia and influenza in the autumn to which a special section of this report has been devoted. The summer season, however, may well be described here.

The highest rate for the summer season is seen from Table 27, (see also Chart XXVI) to be at Camp Las Casas which is located in Porto Rico. The admission rate amounted to 55.4. The record for Las Casas is limited to nine weeks as the camp was not opened until the first week in July. Of the camps for which there is a complete record of twenty-two weeks, Dodge stands first with a rate of 38.2. This is 11 higher than the Dodge rate for the previous winter. During the winter there were six camps with rates higher than that of Dodge and four camps higher that that of Las Casas.

The higher rate at Las Casas is readily explained by the newness of the camp and the assembling of recruits. Most of this pneumonia occurred prior to the middle of August. The measles epidemic followed after the peak of the pneumonia outbreak, a sequence which has rarely been met with at other camps. Although Camps Dodge, Funston, Gordon, Devens and Custer occupied a relatively high position in the summer table which is contrary to their position the previous winter, still for the most part it is the camps of southern troops which continue to occupy the upper half of the rate table. Summer pneumonia was for the most part sporadic rather than epidemic, and a good deal of it occurred during April. There was very little during the warm months of the year. In fact Dodge's high rate was due to a rather sharp outbreak during April. If the facts were known we could probably trace most of the pneumonia of the entire period to the entrance of recruits at the camps. However, the admission of new men during the warm summer months is attended with less pneumonia than in the winter season.

The case mortality of pneumonia during the summer averaged less than during the previous winter. There is a variation among the camps from about 7 per cent to 100 per cent. Omitting the last figure, which record is for two weeks only at Syracuse, and omitting a rate of 50 per cent at Camp Greene whose rate is for but three weeks, the highest mortality is at Dodge, this figure amounting to 33 per cent. The summer pneumonias were for the most part, lobar rather than bronchial. Thus at Dodge of 40 cases occurring between August 5 and September 3 and of which 33 were carefully investigated, it was found that 26 were lobar pneumonia and only one primary bronchopneumonia. It may further be noted that there was but one instance in which two cases were reported from the same company, all other cases being scattered throughout the camp. Of the 33 cases which were inquired into, 25 followed an attack of either cold, grippe, bronchitis or influenza.

Funston is second in the table with a rate of 37.2. The pneumonia which occurred

TABLE 27

PNEUMONIA—FIVE SUMMER MONTHS

Week Ending April 5, 1918, to August 30, 1918

Annual Admission Rate per 1000 for All Troops in U. S.....14.8

ORDER	CAMP	AVERAGE STRENGTH IN THOUSANDS	NUMBER OF ADMISSIONS	ANNUAL ADMISSION RATE PER 1000	NUMBER OF DEATHS	PER CENT CASE MORTALITY
1	Las Casas*	12.8	123	55.4	17	14.
2	Dodge	31.2	505	38.2	168	33.
3	Funston	25.1	395	37.2	75	19.
4	Gordon	36.4	533	34.1	118	22.
5	Wheeler	23.8	290	28.8	43	15.
6	Travis	31.2	380	28.7	64	17.
7	Devens	36.1	409	26.7	46	11.
8	Cody	24.5	272	26.2	38	10.
9	Pike	36.5	379	25.8	104	27.
10	Custer	26.5	264	23.5	48	18.
11	Jackson	33.4	325	23.0	59	18.
12	Bowie	19.1	156	19.3	19	12.
13	Taylor	34.7	248	18.9	52	21.
14	Beauregard	22.1	173	18.4	15	8.7
15	Sevier	19.5	143	17.3	19	13.
16	Lewis	34.2	235	16.2	34	14.
17	Logan	15.1	101	15.9	7	6.9
18	Johnston	17.6	97	13.0	8	8.2
19	Sherman	32.8	172	12.4	47	27.
20	Shelby	20.5	99	11.4	11	11.
21	Upton	34.5	163	11.2	35	21.
22	Fremont	19.9	92	10.9	17	18.
23	MacArthur*	15.5	47	9.3	6	13.
24	Greene*	7.5	4	9.2	2	50.
25	Grant	36.4	139	9.0	39	28.
26	Meade	36.3	138	9.0	22	16.
27	Sheridan	15.9	60	8.9	15	25.
28	Wadsworth	21.7	80	8.7	11	14.
29	McClellan	18.5	64	8.2	6	9.4
30	Kearny	19.4	64	7.9	6	9.4
31	Lee	42.5	134	7.4	19	14.
32	Dix	46.1	110	5 6	21	19.
33	Hancock	25.5	50	4.7	6	12.
34	Greenleaf*	17.7	11	2.7	2	18.
35	Syracuse*	13.5	0	0	1	100.+

*Las Casas—9 weeks—Week ending July 5 to Aug. 30.
*MacArthur—17 weeks—Week ending May 10, to Aug. 30.
*Greene—3 weeks—Week ending Aug. 16 to Aug. 30.
*Greenleaf—12 weeks—Week ending June 14 to Aug. 30.
*Syracuse—2 weeks—Week ending Aug. 23 to Aug. 30.

between June 15 and August 15 and which amounted to 103 cases, was confined for the most part to the June and July draft of Louisiana and Oklahoma negroes. The following table is interesting in this connection. The figures represent the number of cases per thousand strength during the period above mentioned:

JUNE DRAFT		JULY DRAFT	
White men	0	White men	.3
Missouri negroes	0	Missouri negroes	1.
Oklahoma negroes	4.	Kansas negroes	1.
Louisiana negroes	2.6	Mississippi negroes	4.

In the June and July drafts there were received 27,000 white men, who furnished four cases of pneumonia from June 15 to August 15. During the same period, 12,000 colored draft men provided 83 cases of pneumonia.

The sporadic nature of the pneumonia during the summer is borne out by testimony from many camps. Fremont reported that of 78 cases, all of which were primary pneumonia, no two cases occurred among men of the same company. Gordon stands next to Funston with a rate of 34.1. During the entire summer season there were 533 cases of pneumonia reported. In the period from June 1 to September 8 there were 257 cases of pneumonia, all of which were lobar. Only four of these followed measles.

Camp Jackson states that most of the cases during the summer occurred in newly drafted men and it was attributed to their change of environment. These men came from rural communities. They developed a "barracks cough" which seemed to make them more susceptible to pneumonia. At Grant, pneumonia was confined for the most part to the 161 Depot Brigade and the colored organizations. From June 1 to September 10 there were 85 cases of pneumonia at Beauregard. Eighty of these were lobar. Of the 85, 70 were primary, three followed measles, five followed colds, grippe or bronchial influenza and four were postoperative. Sixty-three of the 85 cases had seen less than one month's service. The proportion of bronchial pneumonia among camps during June, July and August was as follows:

Cases of Pneumonia

CAMP	LOBAR	BRONCHO	PER CENT OF BRONCHO-PNEUMONIA
Shelby	41	40	49.
Sevier	31	21	40.
Meade*	23	15	40.
Fremont	51	27	35.
Sherman	54	12	18.
Beauregard	80	5	5.9
Dodge	31	2	5.7
Gordon	257	0	0

*July and August only.

Beauregard's case illustrates the general trend of the pneumonias from winter to summer. From September, 1917, to May, 1918, inclusive, 61 per cent of pneumonias were bronchial. In the three warm summer months, as shown above, the bronchial pneumonias amounted to but 5.9 per cent.

The mortality from each of the two forms of pneumonia in the warm summer months we can judge only from the figures available for a few camps, thus:

CAMP	LOBAR PNEUMONIA			BRONCHOPNEUMONIA		
	Cases	Deaths	% Case mortality	Cases	Deaths	% Case mortality
Fremont	51	8	16.	27	4	15.
Sevier	31	4	13.	21	3	14.

There were but three deaths among 85 pneumonias at Beauregard. One of the deaths was due to lōbar pneumonia as determined by autopsy. The form of the other two is not stated.

Meade had one death among 38 pneumonias during July and August.

Sherman for the same period reported 4 deaths among 66 pneumonias. The division of the deaths among the two forms of the pneumonia is not given.

We may sum up this scattered and scanty evidence with the statement that summer pneumonia was for not far the most part lobar in type and relatively more fatal in character.

We can not conclude this brief discussion of the spring and summer pneumonias

without quoting from a report on the subject by Major Woolley of Camp Devens. The report is for the brief period from August 1 to 28 and discusses the causes of pneumonia among 34,406 white men and 3950 negroes. There were 20 cases among the white and 68 among the negroes. The white incidence amounts to an anuual rate per 1000 of 7.5; that for the blacks to 226. One death occurred among the negro cases. This case mortality rate of less than 2 per cent for the entire group is astonishingly low.

The colored troops were mostly from Florida. They differed from the whites in having experienced a change of climate and although this was the warm season, the changes from day to day and the change from warm days to cool nights were different from what the colored troops had been accustomed to. Coupled with this factor was the shortage of bedding. Each man was furnished with a cotton comforter which was adequate for northern men, but not sufficient to keep the southern man warm on the cool nights of which there were many.

The colored men were worked harder than had been their custom in civil life and carelessness in cooling off after severe physical exertion was another factor that may have lowered their resistance.

Chronic infections were widely prevalent among the colored troops. Of 50 negro pneumonia patients, 25 gave histories of previous malaria, 31 had gonorrhea, 11 admitted syphilis, and hookworm had been actually demonstrated in five. In 21 cases two or more of these infections were present. Of the white cases one gave a malarial history, one of gonorrhea, one of lues. None had hookworm. Ten of 50 colored men had had pneumonia before. Four of the white cases had had pneumonia previously. The proportion of previous pneumonia was thus the same in both. Both white and colored men lived in overcrowded quarters. Certain barracks intended for 216 men were occupied by over 300 and in one case by 376.

In the three respects listed above—exposure, fatigue, and constitutional well-being—the two races differed. It is Major Woolley's belief that entirely apart from the question of the prevalence of infecting bacteria, this combination was responsible for raising the sick rate among the negroes to ten times the figure of the whites.

Further analysis of the causes of pneumonia will appear in the discussion of influenza and its complications, which is being prepared for the volume on *Communicable Diseases* to appear in the *Medical and Surgical History of the War.*

THE ROLE OF THE PATHOLOGIST IN THE PRACTICE OF MEDICINE*

By Wm. Carpenter MacCarty, M.D., and Albert Compton Broders, M.D., Rochester, Minn.

THE definition of pathology clearly states that pathology is the science of disease, its nature and cause. It being a comparatively recently developed science, its importance as a routine clinical diagnostic adjunct has only begun to be realized. In fact the pathologist has been generally thought of by most clinicians as an interesting luxury—a corrector or confirmer of diagnoses after the patient is dead. This statement seems strange to pathologists who have conscientiously devoted their lives to training students and investigating intricate problems of disease. Some pathologists undoubtedly bear a close relation to patients, but the majority of pathologists, throughout the world, for technical reasons, spend most of their time apart from patients and practical clinicians. Few are clinical consultants who have to do directly with living patients and few general clinicians consider them worthy of the status of clinical consultant.

In the early history of medicine, clinicians knew all that was known of pathologic conditions and processes simply because little was known about them. As opportunities for increased knowledge of disease arose as a result of detailed postmortem examinations and other laboratory procedures connected with the study of disease, some one individual was kept busy dealing with the material and technic associated with such opportunity. That individual was known as the pathologist—the clinician dealt largely with histories, symptoms, signs and treatment.

While these are general facts concerning the functions of these two important members of the medical profession, each is modifying his functional efficiency; the clinician is studying pathologic conditions and processes and the pathologist is gradually but perhaps too slowly beginning to associate himself intimately with the patient and his clinical colleagues.

Scientific efficiency can only be obtained by one method; namely, that of having the clinician intimately associate himself with the work and judgment of the pathologist without doing detailed laboratory technic and the pathologist associate himself with the work and judgment of the clinician in his study of the patient without doing routine technical procedures for which the clinician is especially trained. Each of these specialists has more than he can do, but together they can readily do more for the patient and science than either one alone. This is cooperative specialism which reveals itself in the accompanying figures which represent the part played by a group of clinical and research pathologists working intimately with a group of clinicians. The statistics represent the laboratory reports made on 49,083 patients registered during the year 1918.

*Read before the American Association of Pathologists and Bacteriologists, June, 1919, and the Southern Minnesota Medical Association, June, 1919.

I. Metabolic rates determined			2,875
II. Gastric analyses made			9,560
III. Bacteriological and serological examination:			
	Sputum	1,989	
	Stools	2,488	
	Cultures (general)	1,510	
	Smears (general)	491	
	Vaccines	120	
	Wassermanns	21,994	
	Blood grouping	583	
	Skin tests	441	
	Special examinations	1,736	
	Stains for B. tuberculosis (urine)	968	
	Positive tuberculosis sputum	299	
	Total number		32,619
IV. Urine examinations:			
	General	7,981	
	Functional	6,891	
	24-hour specimens	47,784	
	Ureteral specimens	3,591	
	Special examinations	193	
	General and functional	2,586	
	Total number		69,026
V. Blood examinations:			
	Complete cell counts	2,337	
	White cell counts	939	
	Other tests (specials)	722	
	Hemoglobin determinations	5,614	
	Incomplete counts	20,573	
	Coagulation and special examinations	538	
	Total number		30,723
VI. Miscellaneous examinations			83
VII. Autopsies			530
VIII. Electro-cardiographic record			1,285
IX. Fresh tissue examinations (living patients)			11,147
Total number of pathologic reports			157,848

The last figure (157,848) represents the number of laboratory reports on 49,083 patients and not the number of laboratory examinations, for each involves frequently many examinations and tests.

The pathologist's reports represented by these figures have one or more of the following values to the patient and clinician:

1. *They confirm the diagnosis of which there might be a clinical suspicion,* i. e., the clinician suspects that an ulcer of the lip or stomach is malignant and the microscopic examination confirms the suspicion.

2. *They actually make the diagnosis in which there is no clinical diagnostic suspicion,* i. e., the clinician obtains a history of a gastric lesion, which, upon exploration appears to be an extensive carcinoma—microscopic examination reveals the gastric lymphatic glands inflammatory. The patient has a negative preoperative Wassermann reaction and the specimen after the resection for the obstructive mass reveals an inflammatory condition which turns out to be syphilitic, confirmed by a positive postoperative Wassermann reaction. The diagnosis and prognosis are considerably altered.

3. *They recognize accessory pathologic conditions,* i. e., the clinical diagnosis of myomata of the uterus is followed by subtotal hysterectomy and a car-

cinomatous growth is found in one of the horns of the uterus, or a young female has a large mammary cyst but after its removal, a small carcinoma is discovered in the vicinity of the cyst by the pathologist. Such accessory findings alter the degree of operative intervention and change the prognosis.

4. *They correct the clinical diagnosis*, i. e., the clinician makes a diagnosis of, and the surgeon removes a sigmoid mass which the pathologist discovers is simply a sigmoid peridiverticulitis or excises an ulcer of the lip for epithelioma, and it is found to be a syphilitic ulcer or starts to remove an appendiceal fistula and the pathologist, from the secretion, shows the presence of actinomyces. The last condition should alter the surgical procedure because the patient would undoubtedly still have a postoperative fistula.

5. *They confirm the positive clinical diagnosis*, i. e., the clinician makes a diagnosis of syphilis from the presence of a small scar on the prepuce; the patient gives no history of primary or secondary syphilitic lesions but admits the great possibility and the pathologist reports a positive Wassermann or the clinician diagnoses an endocarditis and streptococci are found in the blood or there is a chronic inflammatory condition of the urinary bladder with pus in the urine and the clinician makes a diagnosis of tuberculosis from the history and the presence of an old tuberculous focus in the lungs—the pathologist demonstrates the B. tuberculosis in the catheterized ureteral urinary specimen, or a patient has a profuse hemorrhage from the uterus after menopause, there being no pelvic mass; a diagnosis of malignancy is made and the scrapings reveal a carcinomatous polyp.

6. *They determine the degree of the process of disease*, i. e., the surgeon makes a gross diagnosis of carcinoma of the stomach and finds a nodule in the liver which he thinks is a metastasis, in which case he probably would not resect the stomach but the sections from the nodule reveal an inflammatory condition which may or may not surround a gallstone which had become ulcerated into the liver substance. The degree or extent of the disease is determined and the surgeon is led to resect a portion of the stomach.

A patient has a pathologic kidney and the degree of function is determined by the phenolphthalein and blood-urea tests.

7. *They determine the physical status of the patient preparatory to possible operation*, i. e., a patient receives a diagnosis of "exophthalmic goiter" or hyperthyroidism. The metabolic rate is greatly above normal which indicates a poor surgical risk or it is slightly above normal and indicates a good surgical risk.

8. *They help to determine the extent of the operation*, i. e., a young woman presents herself with a nodule in the breast; it is locally removed (never incised) and submitted to microscopic examination. The extent of the operation necessarily depends upon the report. A young patient has prolonged irregular uterine hemorrhage for which a reliable surgeon or clinician would hesitate to advise a hysterectomy. The uterus is curetted and the diagnosis of carcinoma is made, followed by hysterectomy.

9. *They give data for the preoperative, operative, and posthospital prognosis*, i. e., a patient has a slowly developing enlargement of the tibia; there is an enlarged lymphatic gland in the groin. Repeated Wasserman tests are negative. The examination of the gland is of prognostic value.

A patient needs an operation for removal of gallstones, bladder stones, ureteral stones, hypertrophy of the prostate, or carcinoma of the uterus, but the examination of the blood reveals a low hemoglobin and the renal functional test reveals marked anemia and renal insufficiency. The prognosis is somewhat dependent upon these findings.

10. *They determine the cause of death in nonoperative and operative cases,* i. e., in medical or operative cases not previously diagnosed the autopsy frequently clears up the diagnosis.

11. *They determine the cause of death due to false operative judgment,* i. e., patients are sometimes advised to have operations and die because of the presence of other pathologic conditions which are recognized only at autopsy. Operative procedures sometimes lead surgeons to work with tissues, the vitality of which or the character of which is such that they will not survive such treatment. This has been seen rarely in resections in which the tissues were so disturbed by anemia, inflammatory reactions or carcinoma that sutures did not functionate. The cause of the subsequent peritonitis is revealed at autopsy.

12. *They determine faulty operative technical causes of death,* i. e., unintentional ligation of ureters or ligation of necessary intestinal blood vessels or improperly placed intestinal anastomoses causing death are revealed at autopsy.

13. *They assist in determining causes and methods of surgical infection,* i. e., routine bacteriologic examinations of operative wounds, operative materials, contents of operated organs or tissues lead to a better control over possible infections.

14. *They assist in clinical, surgical, and laboratory research.*

These simple examples are but a few of many instances of the relationship of laboratory procedures and judgment to efficiency in the practice of medicine. In this series each patient averaged 4.2 laboratory reports each of which represents usually many examinations. Of these reports 45 per cent were of necessity microscopic examinations. The figures represent the relationship of the pathologist to general patients and may be supplemented by the following figures illustrative of the relationship of tissue pathology alone, to diagnosis and surgical operations.

Of the 49,083 registered patients, 22.7 per cent produced diagnostic and surgical tissue specimens for examination and 3.5 per cent of all patients had specimens of tissues removed solely for diagnostic purposes. Of the latter, 83 per cent were of necessity microscopic diagnoses.

In the series of operative patients during the same period there were 11,149 tissue reports made, 16.7 per cent of which were of necessity microscopic examinations. This figure varies from 15 per cent to 30 per cent in different series which have been studied from year to year. Of the last 14,167 operative cases which produced tissue specimens (61 per cent of all operative cases) 20 per cent required a necessary microscopic diagnosis although all specimens were examined microscopically routinely.

In conclusion it should be stated that the statistics which have been briefly presented here should be sufficient to show the medical profession that laboratory methods which were formerly considered principally of postmortem and research interest have become an essential part of efficient routine practice of medicine.

ENCEPHALITIS LETHARGICA

By C. M. Stafford, A.M., M.D., Detroit, Mich.

IN THE April issue of this Journal, Vaughan gives a most thorough synopsis of what has recently appeared in current medical literature concerning a new syndrome known by the name of "encephalitis lethargica."

This peculiar and apparently rather rare disease, according to the observations of practically every one who has come in contact with it, is characterized by apathy and drowsiness, sometimes amounting to real coma, as its main features. Other symptoms vary in different cases and include palsies of the third pair of cranial nerves, meningismus, general bodily rigidity, urinary retention, cyanosis, restlessness, delusions and hallucinations, accompanied by mild fever.

The mortality seems to be about 50 per cent. Postmortem, the findings are quite typical. Macroscopically, there is congestion of the meninges and scattered hemorrhages in both white and gray matter. Microscopically, there is found a small-celled infiltration, especially marked about the blood vessels and occurring most numerously in the medulla, pons, and basal nuclei.

The etiology of the condition has not yet been definitely established. From its incidence on the heels of the recent pandemic of influenza, many have thought it to be a peculiar manifestation of this waning infection. By others it has been variously ascribed to a lowered resistance following a previous attack of influenza or as a manifestation of botulism. In favor of its influenzal relationship may be cited its occurrence in its present epidemic form just after we have gone through a world-wide epidemic of influenza. In support of this theory also are the reported epidemics of the symptomatically similar diseases known as "Nono," occurring in the spring of 1890 in Northern Italy and Hungary and here and there throughout Europe, and the "Tübingen sleeping sickness" of 1712, both of which followed pandemics of influenza, and the fact that many patients have given a history of recently having had influenza. Against its direct connection with influenza, however, it may be said that many of the persons affected by this lethargic disease give no history of having had influenza.

Blood counts do not reveal a disturbance of the normal cellular relationships either as to numbers or morphology. The urine is negative. The blood Wassermann is likewise negative. The spinal fluid findings, however, have been rather constant. The fluid very uniformly is found to be under increased pressure and escapes from the cannula in a jet or with rapid dropping. Examined by the Wassermann reaction it is found to be negative. The globulin is increased as are also the cells, the latter averaging from 10 to 100 per cu. mm. and are of the lymphocytic type.

That the condition is due to a definite infection of some kind or other would seem most probable. In January, 1919, the London Board of Health made this disease reportable in the belief that it is infectious in character. Indeed, von Economo, who by his monograph has given the subject more thorough study than any other, states that the virus is nonfilterable through Berkefeld filters,

differing in this respect from that of poliomyelitis. He states also that the disease can be transferred to apes, and von Wiesen succeeded in isolating a diplostreptococcus from such an infected ape which he believes to be the cause of the disease. So far as I have been able to ascertain, however, this organism has not been isolated directly from the human.

On March 23, last, I was called to see my first case of this kind. The patient, a man 36 years of age, a German by birth, and a mechanic by occupation, married, and the father of four children, had taken to his bed ten days previously. The wife furnished me with quite a complete history which he himself corroborated. Up to the present time, aside from "colds," he had never had any illness to speak of since childhood. He had not had influenza, neither had any one in the household had it.

On March 13, following several days of malaise, he had taken to his bed because of the increasing languor. On March 15, he began to complain of pain over the region of the left frontal sinus, from whence it radiated over his scalp. On the 17th, the pain in the head still continued, but he also began to have severe pain in the left arm and over the manubrium. On the 20th, the pain had extended into the right arm also.

I had been called on the evening of the 23d. My entry into the room was unobserved by the patient who lay sleeping with occasional paroxysmal twitchings of the hands, fingers, and arms. His breathing was quiet save when interrupted by some quiet, incoherent exclamation. His wife stated that he had been talking in this way for the past two days. His general appearance was that of a not-very-robust man. The skin, lips, and finger nails were slightly cyanotic. The patient roused from his lethargy upon being shaken and spoken to rather loudly. He immediately began to complain of intense pains in both arms and in his chest and stated that he could not sleep. No sooner were the words out of his mouth, however, then he lapsed into sleep again. Evidently, the pains were not sufficient to keep him from sleeping, although he protested that he could not stand the pain and could get no sleep. Examination showed a regular pulse of good volume with a rate of 80. The temperature was 100° by mouth. The pupils were somewhat miotic, regular, and sluggish, but responded to light and accommodation. There were no ocular palsies or rigidity of the neck or extremities. Kernig's sign was negative. Cutaneous and deep reflexes were sluggish.

On March 25, I had him removed to St. Mary's Hospital for observation. There the somnolence continued, although on arousing him he always complained of pain and plead for something to relieve him and make him sleep. On March 25, in the evening the temperature was 99.4°, pulse 76. On the 26th, in the morning it was 100.2°, pulse 82; in the evening, 98.2°, pulse 70. During the next five or six days the temperature oscillated from normal to 100°, but was irregular in type, sometimes up in the morning and down at night and vice versa. After this time the temperature remained normal.

Examination of the urine was negative. A blood count made April 1 showed erythrocytes 4,100,000; whites 8,000. Differential white count showed polymorphonuclears 60 per cent, small mononuclears 21 per cent, large mononuclears 14 per cent, and eosinophiles 5 per cent; hemoglobin 90 per cent; color index .9. A Wassermann of the blood, taken March 31, gave an 0-0-0 reaction.

On April 4, a spinal puncture was made. The fluid was under increased tension, running very freely from the cannula instead of dropping as in the usual case. The fluid was clear with a number of small whitish flocculi. A Wassermann of the spinal fluid was negative; cell count 60 per cubic millimeter and of the lymphocytic type with increased globulin by the Ross-Jones and Pandy methods. With the escape of the first 15 c.c. of spinal fluid, the patient moved his head and said that the pain in his chest and arms had disappeared. Twenty cubic centimeters of spinal fluid were removed. The somnolence was also improved by the puncture, but both pain and somnolence had regained their former status within 48 hours. On April 7, a second spinal puncture was made with similar results, namely, relief of pain, the spinal fluid under pressure, and similar cytologic and globulin findings. April 15, a third spinal puncture was made and on this occasion the fluid was found to be under average normal pressure and of normal macroscopic appearance. A cell count and globulin estimation showed no increase and on April 19 the patient was able to leave the hospital, although still complaining of some pain in the chest and arms and of great weakness.

The highly interesting point in relation to this case is in regard to the bacteriologic findings of the specimens of spinal fluid. A smear of the centrifugalized sediment of the first puncture showed, in addition to lymphocytes, a number of rather large diplococci. Cultures were made on ascitic agar, Loeffler's media, blood agar, and in ascitic broth, but with negative results. So much time was lost in making these cultures that we felt the organism observed had probably been lost. The fluid from the second spinal puncture also showed, under the microscope, this same diplococcus, but cultural attempts in these same aforementioned media were likewise negative. In an endeavor to secure a culture at any cost, both the first and second specimens of spinal fluid were placed in the incubator overnight at 37.5° C.

The following morning numerous minute flocculi were observed throughout both tubes. They were placed in the centrifuge and thrown down. By inoculating ascitic agar slants with this centrifugalized sediment a sparse growth was obtained, which increased as it was repeatedly transplanted. The organism grows rather poorly on plain agar. The colonies on this media resemble streptococcus colonies, except that they are more delicate and slightly smaller.

The organism is a Gram-positive diplococcus, frequently occurring in short chains of three or four loosely-joined cocci. It stains, but rather poorly, with all common laboratory dyes, some organisms being deeply stained and others lightly. It produces no capsule. In smears from 48-hour cultures, it was observed that the chains show a tendency to divide longitudinally, i. e., a distinct and continuous cleavage can be noted, extending throughout the length of the short chain of cocci. This probably accounts for the clusters of organisms, resembling staphylococci, which are commonly encountered in smears from older cultures.

Growth on blood agar plates did not produce any hemolized areas or greenish zones. The inoculation of a guinea pig intracardially with one-half the growth on an ascitic agar slant failed to produce any ill effects. A rabbit, inoculated intravenously with two large doses, 7 days apart, the first consisting of the growth of one ascitic agar slant suspended in saline solution and the sec-

ond the suspended growth of three agar slants, apparently developed no illness, but the presence of agglutinins was demonstrated. Another rabbit inoculated intraspinally with the growth from an ascitic agar tube suspended in salt solution showed no ill effects.

The following results were obtained from 24 hours of growth on the media tabulated:

Medium	*Acid*	*Gas*
Litmus Milk	No	No
Nutrose Broth	No	No
Saccharose Broth	Yes	No
Levulose Broth	Yes	No
Mannite Broth	No	No
Lactose Broth	No	No
Glucose Broth	Yes	No
Inulin Broth	No	No

The growth on ascitic agar is slightly heavier than the ordinary streptococcus growth and somewhat whiter. The culture is being kept alive by frequent transplantations and with repeated transplantation has become heavier, so that macroscopically it now no longer looks like a streptococcus growth, nor is it so heavy as a staphylococcus growth. Under the microscope its morphology has not changed.

We have not yet determined its pathogenicity for apes, but hope to determine this point in the near future. Pending this determination we can only state that in two successive withdrawals of spinal fluid from this case of epidemic encephalitis, a diplo-streptococcus was isolated in pure culture.

LABORATORY METHODS

SOME NEW APPARATUS—A COMBINATION TAMBOUR AND MEMBRANE MANOMETER AND A MODIFIED SPRING MANOMETER*

By D. E. Jackson, Ph.D., M.D., Cincinnati, Ohio.

In 1891 Hürthle[1] described a membrane manometer of which various modifications have since been made. The combination here described is designed to save expense, and at the same time to furnish a membrane manometer of great sensitivity, and with a wide range of adjustments. This is accomplished by using one base stock with removable bowls for both tambour and manometer. In Fig. 1 the instrument is shown complete as used for recording blood pressure. The manometer bowl can be adjusted back and forth to change the magnifica-

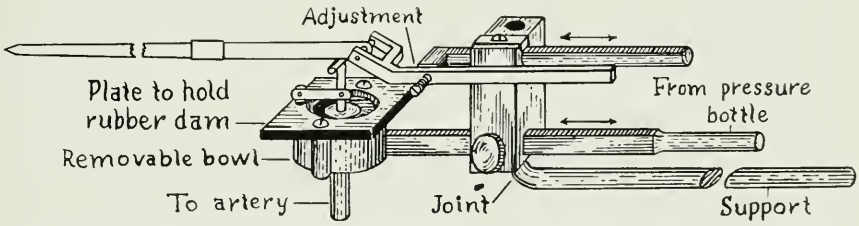

Fig. 1.—Combination tambour and membrane manometer (arranged as a manometer).

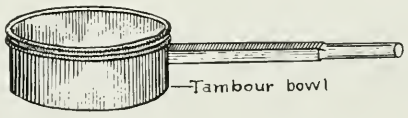

Fig. 2.—Extra bowl to be substituted when the instrument is used as a tambour.

tion of the tracing, or the bowl can be removed from the base stock entirely and a special tambour bowl (Fig. 2) can be substituted in its place, thereby forming a complete tambour. Three different sizes of tambour bowls are provided so that the instrument can cover a very wide range of work. The rubber membrane of the manometer bowl is held in place by a thick metal plate which is attached to the bowl by two small screws. When these screws are removed the plate can be lifted up and a new membrane inserted. A large circular opening cut in the center of the plate permits the lower surface of a small circular disc to rest on the the rubber membrane. Attached to this disc is the special lever mechanism which transmits the impulses reaching the interior of the bowl to the writing lever. The mechanism to which the writing lever is hinged can also be readily adjusted in two directions, back and forth and up and down.

*From the Department of Pharmacology of the University of Cincinnati Medical College, Cincinnati, Ohio.

A further very serviceable feature which the instrument possesses is involved in the manner of the attachment of the supporting rod to the base stock. The end of the supporting rod is turned upward at an angle of ninety degrees at the point of its insertion into a one-fourth inch hole passing perpendicularly through the base stock. A set screw (not seen in the figure) firmly clamps the tambour on the supporting rod. Thus the tambour may be rotated to any desired angle in a horizontal plane. This is frequently a great convenience when one desires to arrange a number of instruments to write simultaneously on a drum.

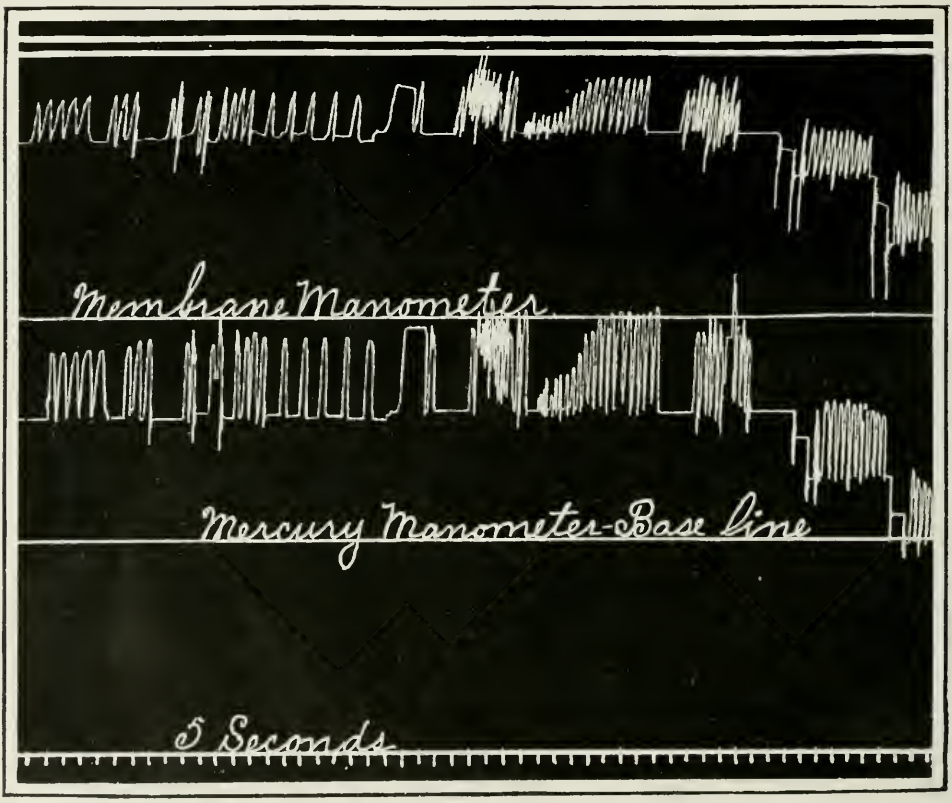

Fig. 3.—Tracing made mechanically to show the comparative action of the membrane manometer and a mercury manometer.

Fig. 3 shows a tracing in which the upper pressure curve was made by the membrane manometer, while the lower pressure record was made synchronously with a mercury manometer, both instruments being directly connected together by rubber tubing. In this manner the membrane manometer can easily be calibrated. The curves here shown were made by mechanically varying the pressure by hand simultaneously in the two manometers.

Fick[2] described a special form of spring manometer in 1864. The instrument shown in Fig. 4 is considerably modified from the original Fick design, and is also simpler in construction. This instrument is made of brass and the parts are soldered together. Consequently mercury must not be allowed to come

into contact with the manometer as the formation of the mercury amalgam would destroy the instrument. And it is also desirable not to allow strong solutions of sodium citrate or sulphate to stand for long periods in the instrument as these salt solutions tend to slowly decompose the solder.

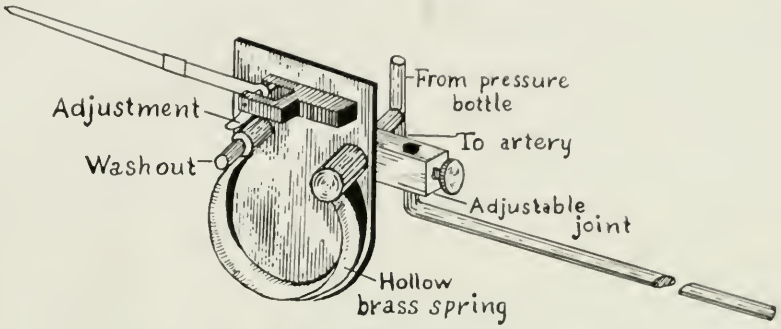

Fig. 4.—Modified Fick spring manometer.

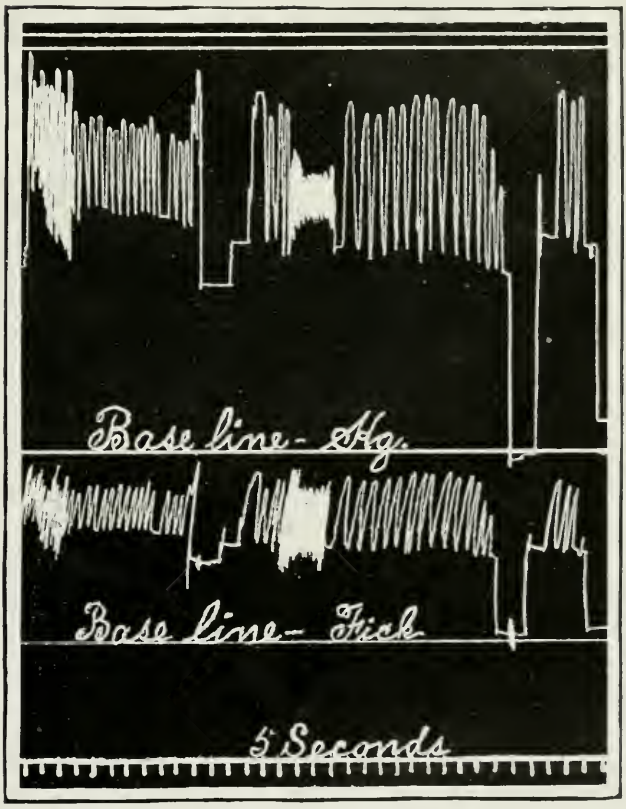

Fig. 5.—Tracing made mechanically to show the comparative action of the spring manometer and a mercury manometer.

At the rear of the instrument is a T-tube, the straight side of which stands perpendicularly. The upper end of this tube connects with the pressure bottle, while the lower end attaches to a tube leading to the artery. The side arm of the T-tube passes through the instrument into a hollow cylinder attached to the

front side of the manometer. From this cylinder a large, flattened, curved, hollow spring made of very thin brass passes circularly around the lower part of the instrument. At the opposite end of the spring is attached a second smaller hollow cylinder from which a washout tube extends. The purpose of this washout tube is to allow the anticoagulating solution to be passed through the instrument and thus displace the air before connecting the manometer to the artery. A small rubber stopper is used to close the end of the washout tube.

The magnification by the writing lever can be controlled by shifting up and down the end of the block to which the lever is hinged. This is accomplished through the action of a set screw (not seen in the figure) which passes through the instrument from the rear. The manometer can be rotated to any desired angle in a horizontal plane by means of the special method of attaching the supporting rod.

Fig. 5 shows a tracing taken simultaneously with the spring manometer (lower curve) and a mercury manometer (upper curve), both instruments being directly connected together by means of rubber tubing filled with salt solution. The tracings were made by mechanically varying the pressure in the two manometers by hand. In this manner the spring manometer can easily be calibrated.

These instruments can be obtained from the Max Wocher & Son Co., of Cincinnati, Ohio.

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EXPERIENCES IN THE PURCHASE OF BASIC FUCHSIN*

By F. L. Mickle and M. B. Sherwood, New Haven, Conn.

EXPERIENCES encountered by this laboratory in purchasing basic fuchsin are here recorded in an effort to learn whether similar difficulties have been encountered by workers in other laboratories.

In March, 1918, one hundred grams of basic fuchsin were purchased from a well-known chemical supply house for use in the preparation of Ziehl-Neilsen carbol-fuchsin staining solution for demonstrating tubercle bacilli in sputum. From this stain a carbol-fuschin solution was prepared which appeared to be of proper concentration and which stained well. However, on standing over night a heavy precipitate settled out, leaving a thin, red, supernatant liquid entirely unsatisfactory for staining tubercle bacilli. Repeated attempts to prepare solutions from this fuchsin gave similar results and the stain was returned to the supply house. They found, upon testing it, that the amount of "salt" used in the process of manufacture was "beyond comprehension." One hun-

*From the Bureau of Laboratories, Connecticut State Department of Health.

dred grams of basic fuchsin crystals were furnished in replacement. This crystalline fuchsin precipitated from solutions much as the first had done.

An order was placed with another firm for two hundred grams of basic fuchsin which they guaranteed in the following terms:

> "These are not Grubler's stains, although they are of imported stock. These stains were imported from Germany some time ago in bulk, and came from the same source of supply as the Grubler stains.
>
> "We will guarantee the results produced to be equal to the Grubler, or otherwise the stain may be returned for credit. We have already supplied a large quantity of this stain to a number of laboratories and the reports received are very favorable."

This stain was similar in appearance to the last lot purchased from the other firm and was contained in jars of the same type with identical labels. The company selling this stain had pasted a label with their name and address over the portion of the label where the name of the other firm had appeared.

These last two lots of fuchsin were mixtures of a powdered stain with coarser crystals. It was noticed that the crystals were not readily soluble in alcohol. The product secured from the first supply house was then sifted through ordinary sand sieves and sixty per cent (crystals) was caught on the twenty-mesh sieve, five per cent was retained on the forty-mesh, and the balance passed the forty-mesh. The stain from the other firm gave a similar result. Fifty-one per cent (crystals) failed to pass the twenty-mesh sieve, five per cent was retained on the forty-mesh, and the balance passed this sieve. The crystals retained on the forty-mesh sieve were somewhat soluble in water but practically insoluble in alcohol. Washed free from a coating of the fine powdered stain, they proved to be white. A solution of them, when inverted with hydrochloric acid, reduced Fehling's solution. The polariscope showed that they were crystals of sucrose. The powdered stain passing the forty-mesh sieve appeared to be basic fuchsin and was satisfactory for staining the tubercle bacillus.

The above results were reported to both firms and they have given credit for the stains. One of the firms stated that this product had been obtained from a manufacturer at various times over a period of many months. The original had been found by test to be thoroughly reliable and apparently an unsatisfactory stain had been substituted later by the manufacturer.

A METHOD FOR MAKING GLASS ARTERIAL CANNULAS*

By John A. Higgins, Chicago, Ill.

A PROBLEM, which no doubt is of much concern to the laboratory research worker as well as the pharmacology or physiology instructors, is to be able to keep on hand, or construct at will, an adequate supply of glass arterial cannulas of various sized arterial openings. Heretofore this problem has been looked upon as a rather technical matter and difficulties have been experienced in locating, either directly or indirectly through an apparatus supply house, a skilled glass blower.

The comparative ease experienced, especially at the hands of students, in breaking off the arterial section of the cannulas only adds to the supply problem. This inconvenience experienced of having glass arterial cannulas broken

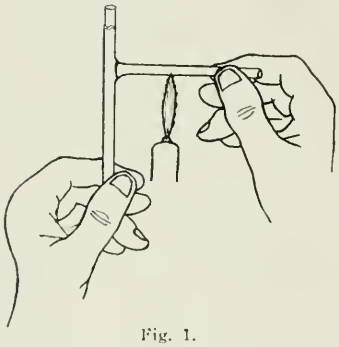

Fig. 1.

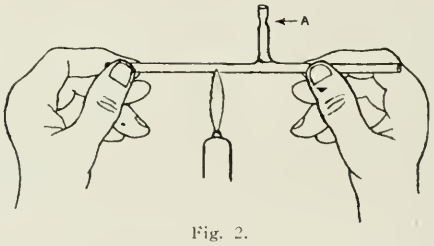

Fig. 2.

Fig. 4.

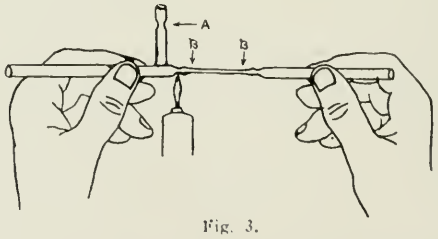

Fig. 3.

off at the arterial opening, can, of course, be overcome by constructing cannulas from brass material. The brass constructed cannulas, however, do not always appeal to the laboratory workers as a substitute for the glass arterial cannula.

While the glass cannula may seem rather difficult for the average person to make, it is possible to make suitable arterial cannulas from glass T-tubes. The most suitable are perhaps made from T-tubes measuring 3 by 6 inches long and with a ¼ inch, inside diameter, opening.

The short, or 3-inch section of the T tube is rotated with the right thumb and fingers in a relatively low blast flame, about two inches from the opened end. When the glass tubing shows signs of softening, at the heated section, then grasp one end of the long, or six-inch, section of the T-tube (see Fig. 1) with the left hand and gently pull apart with both hands leaving a sort of groove

*From the Department of Physiology, University of Illinois School of Medicine, Chicago, Ill.

as shown at *A* Figs. 2 and 3. Some workers do not consider such grooves in a cannula essential, while others utilize them to tie on rubber tubing and thus eliminate connections being separated while under arterial pressure. A filed line is now made around the short length of the T-tube, about 1¾ inches from the opened end. Break off the excess tubing at this point. A second groove it made on one side of the side outlet junction as shown in Fig. 2. The excess tubing need not be eliminated from this section of the cannula as yet. On the ungrooved section of the T-tube, and close to the point where the tubes are connected, gently heat and draw the glass in the same fashion as for making straight cannulas, the opening of this arterial end of the cannula, depending on the length at which the heated tube is drawn out.

Shoulders are now placed on the smaller ends of the drawn tubes, as shown in Fig. 3, using a small needle-like flame. Fig. 3 shows the possibility of getting a straight, as well as an arterial, cannula from the same T-tube. The cannulas are now separated by filed marks, at points *B* Fig. 3, also excess tube ends are now marked with a file and broken off. The angles of the small opening of the cannulas are determined, on a fine grinding wheel, according to personal views. Now heat all edges of the cannulas gently to eliminate any sharp cutting edges. A finished arterial cannula is shown in Fig. 4.

Some laboratory workers seem to be of the opinion that a bulb, at the junction of the cannula proper and the side outlet, is essential to lessening coagulation of the blood, the basis for such view being that the bulb acts as a sort of mixing chamber for the blood and the anticoagulant solution. While such an opinion is perhaps a logical point to bear in mind, still I am inclined to believe that the factor mostly involved is not the presence of a bulbous junction but a proper concentration of a good anticoagulant solution.

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EDITORIALS

The Red Cross as an International Health Agency

RECENTLY the Red Cross organizations of the United States, Japan, England, France, and Italy held a conference at Cannes, France. This conference was attended by men eminent in sanitation and epidemiology from the countries above mentioned. It was supposed at the time that this meeting would be a preparatory one to an international Red Cross conference to be held at Geneva soon after signing the treaty of peace. However the treaty is still in the air, and it may be of general interest to know what was done at Cannes.

Doctor Richard P. Strong proposed that the International Red Cross Societies should inaugurate a movement for the establishment of an organization which will take up the most urgent problems in hygiene and public health and attempt to solve them in the most intelligent manner. He proposed the establishment of a Red Cross International Council and Bureau of Hygiene and Public Health whose principal activities should be as follows:

(1) To call attention to the most urgent and important situations in different parts of the world where medical or sanitary relief is needed, and to the best methods to be employed in extending such relief and by whom it is advisable that such relief should be offered.

(2) To stimulate investigations in relation to problems in public health and carry on original research by the appointment of such commissions when such investigations seem urgent, advisable, and necessary.

(3) To demonstrate and exhibit new discoveries and new methods in combating infectious disease, and methods relating to hygiene and public health.

(4) To collect all important information relating to public health and new methods for the prevention and control of outbreaks of infectious diseases.

(5) To secure accurate knowledge concerning public health institutions, schools, and laboratories, in various countries and the work performed therein.

(6) To standardize and improve public health education throughout the world.

Doctor Strong says: "We may suppose that an epidemic of plague has appeared in Greece, that the disease is spreading rapidly and has passed beyond the control of the local authorities. All countries are menaced from this quarter. Greece calls for aid from other nations as did Serbia when she was stricken with typhus in 1915. The Red Cross in different countries wishes to respond, but without a central international bureau the efforts can not be best coordinated and made most effective. We will suppose that the British Red Cross hastily organizes relief units without reference to what other countries may be planning or undertaking. The French, Italian, and Japanese Red Cross organizations act in the same manner. Other countries follow their example, each unfamiliar with the plan of the others or with the nature of the personnel and equipment to be sent. These units arrive in Greece, each with a more or less indefinite plan of action and with its own commanding officer. The local sanitary authorities having already failed in the suppression of the epidemic are not in a position to assume control. Such a condition actually occurred in Serbia in 1915. Unless some individual who can dominate the situation takes control, confusion, lack of cooperation and inefficient management, or failure is likely to result. At any rate it must be obvious that the most efficient work can not be done unless all the relief units act in cooperation under a central direction and with a definite plan. With the existence of an International Council and Bureau of Hygiene with its machinery for obtaining early information the national Red Cross of each nation could be informed of what it was expected to do, and just what form of relief seemed most desirable and necessary. Methods of procedure could be planned by this body. An interallied board would take charge of the situation and constitute a Bureau of Health in the afflicted country and be able to carry out the task before it in an intelligent manner."

In support of his plan Doctor Strong refers to the successful study of trench fever in the spring of 1918. A commission was appointed to carry out experimental work upon this disease and volunteer subjects were secured. Through this interallied cooperation between the British and American armies the work was successfully accomplished and the method of transmission of this disease discovered. The work was made possible largely through an interallied commission which was appointed on account of the war. In time of peace there would have been no arrangement for similar cooperation, and this should be provided for.

The handling of pneumonic plague in Manchuria in 1910 is another illustration. China became seriously alarmed at the situation, appealed for assistance, and the American Red Cross under the authority of the State Department responded to the appeal. The true nature and method of spread of the disease were determined by several scientific commissions sent by different nations to Manchuria. The proper measures were instituted, the epidemic checked, and entirely stamped out within three months.

Doctor Strong makes clear that the chief activities of the International Council and Bureau in relation to research should be upon the whole not to prosecute original investigations except in special instances, but to stimulate research work in scientific institutions already established in different parts of the world, either by securing to such institutions financial support for such studies or by furnishing increased personnel or by rendering other assistance.

It is proposed for the purpose of carrying out this project that there be established in connection with the League of Nations an International Bureau of Hygiene and Public Health situated in the same city as the capital of the League of Nations. There should be maintained: (1) An office, (2) A division of information, (3) A library division, (4) A publication division, (5) A demonstration laboratory, (6) A museum.

There should also be established in connection with the central bureau departments of: (1) Vital statistics, (2) Prevention of communicable diseases, (3) Sanitation, (4) Industrial hygiene, (5) Child welfare.

The international council should meet every four months in one of the allied countries, and annually at the place in which the central bureau is situated. There should be an executive committee composed of one representative from each country. The director of the bureau should be the chairman of the International Council of Hygiene and Public Health. At least one public health official in each country should maintain an office in connection with the national Red Cross. The International Bureau of Hygiene and Public Health described above should constitute a center where questions of common interest to all humanity would be considered. In this way the duplication of public health activities especially in relation to epidemic diseases should be avoided and greater harmony and more forceful action obtained through the employment of unified and most modern sanitary methods. The bureau will not attempt to duplicate or supplant the work of medical and hygienic institutions already established in different countries, but will attempt to further their interests while utilizing their discoveries. In this way it will constitute an international center of ideas, methods, exchanges, relations, propaganda, etc.

The central Bureau of Hygiene will receive the following information:

(1) All new discoveries and methods of importance in relation to public welfare.

(2) All vital statistics.

(3) Information concerning the prevalence of communicable diseases.

(4) Knowledge concerning special sanitary and hygienic problems in different countries.

The bureau will also act in the distribution of the following:

(1) New discoveries and new methods in relation to hygiene and public health.

(2) Facts concerning the objects, work being performed, and personnel in all public health laboratories.

(3) The text of all national health laws.

(4) All valuable information resulting from a codification of proceedings of health congresses in order that such information may be widely disseminated and rendered available.

The collections of the central International Bureau of Hygiene and Sanitation will consist of a museum, a library, and laboratories. The purpose of the museum will be to demonstrate the progress accomplished in fields of hygiene and public health and to accentuate the importance of discoveries. Models of new available sanitary appliances would be on constant exhibition in the museum. The library should be one for reference, made up largely of journals, periodicals, and monographs. It should be a depository of duplicates of all valuable hygienic publication. Writers upon sanitary subjects should be urged to send their works to this library. The International Hygienic Bureau with its laboratories, library, and museum, with its large collections, should attract workers interested in these subjects from all parts of the world.

It is to be hoped that the Red Cross societies of the various nations that are to constitute the much-discussed League will cooperate and realize something like the plan proposed by Doctor Strong. In this country at least the Red Cross has a great hold upon the people. This has been demonstrated as never before during the war. It has asked for millions and its requests have been duplicated in gifts. If wars happily cease, which is by no means certain at the present writing, there could be found no stronger bond for union between the nations than a common struggle against that enemy of all mankind, disease, and especially epidemic disease. Today we scarcely know the A, B, C's of the science of epidemiology. The time may come when we shall be able to foretell the oncoming of an epidemic with much more certainty than the weather of tomorrow or of next week is now foretold. Besides, when this time comes we shall not only be able to predict the oncoming storm, but we shall be able to greatly mitigate, and possibly altogether avert it.

Centuries ago it was known that epidemic diseases traveled from east to west. This was formulated as an epidemiologic law even before the dawn of the Christian era. It was not then realized that the direction of travel of epidemics was determined by the line of human travel. This is now known to be true. The early epidemics of Asiatic cholera during the first part of the nineteenth century contributed greatly to our epidemiologic knowledge. In 1816 this infection began its first recorded travels and reached countries so remote it could be regarded as pandemic. It traveled slowly at that time before the general use of steam transportation, and did not extend westward beyond the confines of Asia and Africa. To the east and south it visited Borneo, Java, the Philippines, and China. It lingered in various localities for years. In 1826 it began from its home near the delta of the Ganges its second journey. This continued for eleven

years. This time it spread over the greater part of Europe and America. It traveled by different routes, some by land and some by sea. Nothing more was known of this infection outside its own domicile until 1846. The third pandemic reached the farthermost parts of the earth and lasted until 1862. It is estimated that in 1853-54 it killed in France alone 150,000 and it pursued the gold-seeker on his way across the plains to California. The fourth pandemic was in evidence by 1864 and continued until 1875. As the records show, it found 114,683 victims in Prussia alone on this trip. The fifth pandemic began in 1883, spread over the eastern hemisphere and reached New York harbor, but was refused admission. This time the number of victims in European Russia alone is estimated at 800,000. The notable outburst at Hamburg belongs to this period. In 1902 cholera became pandemic for the sixth time. Since that time it has been found in various parts of Europe and has repeatedly reached our own shores, but has never been naturalized. During the great World War it has put in an appearance here and there, but scientific preventive medicine has been able to control it.

In all these excursions, among all kinds and conditions of men, in every degree of civilization, in the tropics of Africa and amid the snow and ice of northern Russia, in the thronged city, and in the emigrant's wagon, with high and low, slave and master, wherever it has traveled, cholera has maintained its individuality and has shown no modification in manner of attack or variation in the symptoms induced in its victims. Its vehicle of transport has been man's body and it has followed the lines of human travel, on foot, on horse or camel, by ox team or stage, by steam on land and sea. The sick and dying have scattered its progeny around the world. The science of preventive medicine has proved the only detective who can trace this criminal, the only officer who can arrest, and the only executioner who may finally remove it for all time from the earth.

What has proved true concerning cholera is largely true of influenza. Even now it has reached the uttermost parts of the earth.

—*V. C. V.*

An Addition to Our Editorial Staff

IT is with pleasure that we welcome to our editorial staff Dr. W. C. MacCarty of the Mayo Clinic. We consider ourselves fortunate in securing the help of this eminent man.

The objects which Dr. MacCarty will attempt to secure in the conduct of his department may be stated as follows:

1. To keep the medical profession posted up to date as to the clinical value of laboratory procedures and the conclusions to be drawn therefrom.

2. To attempt to standardize pathologic terminology and make it more efficient. In doing this he will avoid making unduly prominent his own views, but will treat the subject in a broad way.

3. To stimulate physicians to take up laboratory methods as an essential part of the practice of medicine.

4. He will endeavor to encourage the utilization of laboratory specialists as consultants to those directly engaged in the practice of the profession.

—*V. C. V.*

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ORIGINAL ARTICLES

AN EXPERIMENTAL STUDY UPON THE IMPREGNATION OF CLOTH WITH PEDICULICIDE SUBSTANCES*

By W. Moore, A.B., and A. D. Hirschfelder, B.S., M.D.
Minneapolis, Minn.

THE problem of freeing the soldiers from lice divides itself into two distinct phases:

1. The laundering and bathing procedures for ridding the clothes and the men of lice or eggs already present. These were possible only behind the lines.

2. The use of sachet powders and impregnation of clothes and underwear with substances which would kill, or prevent the growth or even the presence of lice in the clothing. Since in many cases the soldiers were on duty continuously without change of clothing for three weeks or more, this phase of the problem assumed particular importance.

In spite of the very large number of researches, which reaches into the hundreds, that have been published or kept as confidential reports of the various governments since the beginning of the war, many difficulties have remained to be overcome, and it was to aid in this that the present series was undertaken at first under a research fund grant from the Regents of the University of Minnesota and later under the auspices of the Medical Science Division of the National Research Council. The researches upon the growing and breeding of lice, as well as upon conditions governing the laundering and ironing of clothing and the compounding of various sachet powders as well as a pre-

*From the Division of Economic Zoology and the Department of Pharmacology, University of Minnesota. Published with the approval of the director as Paper 177 of the Journal Series of the Minnesota Agricultural Experiment Station.

Read before the Association of American Physicians, Atlantic City, June 18, 1919.

This research was aided in part by a research grant from the Regents of the University of Minnesota and in part by a grant from the Division of the Medical Sciences of the National Research Council who have given permission for the publication of the report.

liminary publication on the testing of a considerable number of substances used in the impregnation of cloth have already been published by one of us[1] and are not a part of the present paper. The entire study is now in press as a University of Minnesota monograph under our joint authorship and the detailed publication will soon appear.

The method at first employed in this research was to spread 1 gram of the substance to be tested upon a piece of cloth such as is used in the soldier's underwear 6×8 cm. in size, allow the substance to evaporate, and to test the duration of its power to kill lice by cutting off small strips at intervals and placing such a strip in a glass vessel in which a number of lice and eggs were kept. The vessel was then kept at incubator temperature and the percentage of the lice which were alive after 12-hour intervals was noted, as well as the ability of the various batches of eggs to hatch out.

In order to be regarded as effectual the substance being tested had to kill 80 per cent of the lice within 12 hours or 100 per cent in 24 hours.

All the lice were fed daily or twice daily upon the forearms of human subjects by Moore and a corps of assistants. That this was no indifferent procedure was shown by the fact that each of the persons doing so, suffered more or less from fever, rash, and glandular enlargement, and a condition somewhat resembling but not indentical with trench fever which has been described by Moore[2] in an article in the *Journal of the American Medical Association* and both of us in an article in the *Archives of Internal Medicine*. The testing of the substances upon the louse was all done by Moore,—the chemical syntheses by Hirschfelder.

The mere evaporation of the substances from the cloth exposed to the air was soon found not to coincide entirely with the disappearance of the substance when worn next to the skin and accordingly simple evaporation was discarded as a criterion and in the present research the substances were tested entirely by wearing a patch of impregnated cloth 6×8 cm. pinned to the undershirt and in contact with the skin of the wearer. These gave a fair indication of the conditions under which the substances would be used in practice and it was also possible to determine from the presence of reddening of the skin under the patch whether the compounds were too irritating to be used.

In the preliminary paper referred to above Moore has described the effects of impregnating the cloth with various lubricating oils, lard oil, fish oil, bone oil, and with various vegetable oils such as cottonseed oil, rapeseed oil and palm oil.

These were effective only in concentrations that would render the clothing so saturated with oil that they could not be worn and were only slightly effective when 1 c.c. to 8 square inches, enough to make the clothing visibly oily, were used.

Organic acids (salicylic, oleic, valeric) were useless. Thymoliodide failed to kill, phenyl iodide was transitory. Pure anthracene was useless but crude anthracene killed in 118 hours.

The metallic salts, copper oleate, zinc stearate, zinc chloride, ferrous sulphate, sodium arsenate in 2 per cent solution and saturated lead acetate gave negative results but saturated $HgCl_2$ killed.

[1] Moore, W.: Jour. Am. Med. Assn., Aug. 17, 1918, lxxi, 530-531.
[2] Moore, W.: Jour. Am. Med. Assn., Nov. 2, 1918, lxxi, 1481-1482.
Hirschfelder, A. D., and Moore, W.: Arch. Int. Med., April, 1919, xxiii, 419-430.

Sulphur was negative. Iodoform which had been used effectively by the British in the N.C.I. (naphthalene 96%, creosote 2%, and iodoform, 2%) sachet powders was of some value, but the naphthalene killed only for 12 hours, though cloth impregnated with alphanaphthol retained its killing power for 360 hours and alphanaphthylamine for 720, after simple exposure to the air. On account of their toxicity the cloth was not worn, so that these figures are not comparable with the figures given when the cloth was worn.

Orthonitraniline which lasted 480 hours is too toxic to man to admit of its use. Heliotropine was found to have retained its killing power after exposure to the air for 528 hours, but on being worn lost it after 24 hours although if mixed with cocoa butter it lasted for 168 hours. This was due to the crystallizing.

The success of British investigators with naphthalene and creosote powders and our own results with cresol indicated that cresol was about the most useful substance, but that it disappeared from the clothing too rapidly to suit the purpose. It was accordingly suggested by one of us (H) that derivatives of cresol preserving the general cresol structure, but diminishing the volatility, might afford the solution of the problem, and on this account a number of cresol derivatives were synthesized.

After methylene di-cresol, cresyl benzoate and the cresyl phosphates and a mixture of di cresyl-ethers and cresyl ketone were found to be ineffective, a systematic study of the halogenated cresols was undertaken. Attempts made to prepare these by most of the methods described in Beilstein's Handbuch gave unsatisfactory results but satisfactory bromination could be secured by using Kopheschaar's mixture of sodium bromate, sodium bromide and hydrochloric acid.

Much better results were secured, however, by a method suggested by Dr. W. H. Hunter, dropping the calculated amount of bromine from a separating funnel directly into glacial acetic acid containing the cresol and a small piece of bright iron wire as a catalyzer. Bromination as shown by titrating a sample with KI and thiosulphate was complete in less than an hour. The mixture was then neutralized, separated, and filtered off, washed first with sodium thiosulphate to remove any excess of bromine or bromine that had entered the hydroxyl group, then with sodium bicarbonate and water and finally filtered or separated off.

Chlorine was introduced by bubbling into the glacial acetic acid solution of cresol in the presence of iron wire until the calculated weight of Cl had been taken up. The substances were otherwise treated in the same way as the bromine derivatives.

Iodine was introduced in saturated sodium bicarbonate solution in the presence of potassium iodide. A series of mono- and di-brominated chlorinated and iodo- ortho- meta- and para-cresols was thus prepared in which the halogen had entered the ring. By this mode of treatment the trihalogen compounds of the metacresol only are formed and no trihalogenated ortho and para compounds were obtained.

Chlorine was also introduced into monobrominated metacresol and in this way a monobrom, monochlor and a monobromdichlormetacresol was formed and in the same way a dibrommonochlormetacresol.

When patches of cloth impregnated with these substances were worn it was found that the monochlor orthocresol had no killing power after being worn 24 hours, and that the dichlor orthocresol killed 100 per cent after being worn 24 hours, but none after 48 hours.

The monoiodoorthocresol was variable and uncertain in its effect, but none of the samples killed more than 40 per cent of the lice after being worn more than 168 hours. The monobromparacresol and the monobrommetacresol lost their killing power after 48 hours, while the dibromorthocresol retained it for 120 hours and the dibrommetacresol for 240 hours. On the other hand, the tribrommetacresol possessed too low a volatility, and though lice were killed during the first 24 hours probably on account of the presence of a lower brominated impurity, after 36 hours the killing power was completely lost.

Evidently the optimum volatility to secure the persistence of louse killing power lay with the dibrominated cresol. An attempt was, therefore, made to prepare chlorbromcresols in order to see whether a still nearer approach to the optimum could be made.

The monochlormonobrommetacresol lost its killing power after 48 hours, and the monochlordibrommetacresol lost it after 48 hours, though it still killed 100 per cent of the lice that were exposed to its action for 36 hours. The dichlormonobrommetacresol, however, preserved its killing power for 312 hours (13 days), thus representing the best compound of the series. This compound which has not been described in literature is a white crystalline compound with a melting point of 62 degrees. When beechwood creosote was treated with two molar parts of bromine a product was formed which still killed after 240 hours. Tricresol treated with bromine naturally forms a mixture of bromocresols probably ranging from the mono- to the tribromcresol in varying amounts. When two molar parts of bromine were added and the mixture purified in the same way as the pure cresols the product possessed killing properties after having been worn for 96 hours. When three bromines were added it did so for 120 hours. A sodium salt of the dibrominated tricresol was prepared by (Moore) treating with an excess of 3 per cent NaOH. This compound possessed a high killing power for 192 hours and a low but persistent killing power for 360 hours.

We have also studied the aluminum, magnesium, and calcium compounds of cresol with a view to preparing insoluble compounds of the cresol derivatives which should be less alkaline than the sodium compounds and should slowly split off the cresol so as to continue its louse killing power. Though the compounds of magnesium and calcium with the halogenated cresols were not prepared it seems probable that these were even better suited than the sodium compounds for the purpose of the research. Since naphthaline was rated next to cresol in the experience of the British, corresponding chlorinated naphthaline derivatives were prepared by the method described by Emil Fischer, but these were less efficient than were the cresol derivatives.

After this series was completed the dibromxylenol, the monobromcarvacrol and the dibromeugenol were prepared by Professor R. A. Gortner.

Both the dibromxylenol and the monobromcarvacrol were much less volatile than the dibrommetacresol and killed just as rapidly. Dibromeugenol, which was

even less volatile than the tribrommetacresol, killed within 20 hours, while the tribrommetacresol failed to kill.

The effect of the monobromcarvacrol did not last any longer than that of the dibromcresol when worn, but the reasons for this were not determined.

The substances, therefore, which were found to be best suited to the purpose were the dibrommetacresol which lasted ten days and the dichlormonobrommetacresol which lasted 13 days; and these compounds seemed to fulfil the requisites of the problem so far as a laboratory trial could demonstrate.

Further pursuit of the problem was rendered unnecessary by the signing of the Armistice.

RELATION OF THE PANCREAS TO THE DIABETIC STATE*

By Dwight M. Ervin, A.B., Cincinnati, Ohio

THE pancreatic diabetic state is a condition characterized by several pathologic changes, absence of glycogen, hyperglycemia, fatty changes, acetone bodies and glucose in the urine; and a lowered respiratory quotient. This condition of diabetes has been ascribed to either of two changes from the normal; first the failure of the body cells to properly oxidize glucose; and second, the inability of the body to "fix" glycogen or a too rapid conversion of glycogen into glucose.

The failure on the part of the body cell to oxidize glucose has never been satisfactorily proved (Knowlton and Starling,[1] Levene and Mayer,[2] Paterson and Starling[3]). Levene and Mayer found that glucose disappeared more rapidly from a muscle preparation to which pancreatic extract had been added than from one in which no pancreatic enzyme had been placed. Yet the later work of Patterson and Starling[3] pointed rather to the fact that in the pancreatic extract preparation the large quantity of glucose that disappeared was converted into a nonreducing sugar, for if hydrolysis was carried on (1 per cent hydrochloric acid) the entire difference could be recovered.

The following experiments were performed to test the glucose consumption in the diabetic animal. The diabetic condition was produced by removal of the pancreas:

Experiment 1.—A well-fed dog of about 18 K. was used. Under ether the femoral artery and vein were exposed and a sample of blood taken from each, Sample 1 from the artery and Sample 2 from the vein. The leg was then sewed up and the pancreas removed. At the end of the sixth hour the dog was again placed under ether and the femoral artery and vein reopened. A sample of blood was again removed from each, Sample 3 from the artery and Sample 4 from the vein.

The glucose analysis of each sample gave the following:

Sample 1.—Femoral artery, before removal of pancreas	0.177%
Sample 2.—Femoral vein, before removal of pancreas	0.141%
Difference = normal glucose consumption of leg	0.036%

*From the Department of Pathology of the University of Cincinnati, Cincinnati, Ohio.

Sample 3.—Femoral artery, after removal of pancreas	0.260%
Sample 4.—Femoral vein, after removal of pancreas	0.225%
Difference = Diabetic consumption of glucose by leg	0.035%

Urine after removal of pancreas and at the time Sample 3 and 4 were taken glucose 1.67%.

During the passage of the blood through the leg in a normal condition the glucose concentration was reduced from 0.177% to 0.141% by tissue utilization. In the diabetic state the reduction was the same. In the normal it was reduced 0.036%, in the diabetic it was reduced 0.035%. The glucose consumption was not interfered with in any manner.

Experiment 2.—A rabbit (2 K.) well fed on carrots, greens, and lettuce was placed under ether and blood removed from femoral artery and vein, Sample 1 from the artery and Sample 2 from the vein. The pancreas was then removed. In one hour the rabbit had recovered from the anesthetic. The urine reduced Fehling's solution. At the end of the sixth hour the reduction was strong. Ether again was given and blood taken from the femoral artery and vein. Sample 3 from the artery and Sample 4 from vein.

The glucose analysis of each sample

Sample 1.—Femoral artery, before removal of pancreas	0.130%
Sample 2.—Femoral vein, before clamping vein of pancreas	0.160%
Difference = normal glucose consumption of leg	0.036%
Sample 3.—Femoral artery, after removal of pancreas	0.270%
Sample 4.—Femoral vein, after removal of pancreas	0.240%
Difference = diabetic consumption of glucose by leg	0.035%

Before removal of the pancreas the sugar of blood was reduced in its circulation through the leg by 0.036%. After depancreatization it was reduced 0.030%. A difference of 0.006% which is within the limits of error.

Experiment 3.—While under ether a dog's femoral artery and vein were exposed and the large pancreatic vein found. The smaller veins were tied off. A glucose solution (20 c.c. of 18%) was injected into the ileum. After ten minutes blood was taken from femoral artery and vein, Sample 1 from artery and Sample 2 from vein. The pancreatic vein was then clamped off gently and after an interval of ten minutes blood Sample 3 was taken from the femoral artery and blood Sample 4 from femoral vein. The vein of the pancreas was then unclamped and after another interval of ten minutes blood Sample 5 was taken from the femoral artery.

Analysis of the glucose in each sample

Sample 1.—Femoral artery, before clamping vein of pancreas	0.188%
Sample 2.—Femoral vein, before clamping vein of pancreas	0.160%
Difference = normal consumption of glucose by leg	0.028%
Sample 3.—Femoral artery, after clamping vein of pancreas	0.236%
Sample 4.—Femoral vein, after clamping vein of pancreas	0.208%
Difference = consumption of glucose by leg in diabetic state	0.028%
Sample 5.—Femoral artery after unclamping pancreatic vein	0.190%

From Sample 5 we have a check upon the effect of ether. The rise in arterial blood sugar from 0.188% to 0.236% was due to the clamping of the pancreatic vein. Here again although we have a decided rise in the percentage of sugar in the blood on the clamping of the vein of the pancreas, we have the same reduction in the arterial sugar on its flow through the leg. If in the condition of diabetes there is a underoxidation of glucose the percentage of glucose in the blood should remain the same after it flows through the leg. But in the three preceding experiments the decrease in the percentage showing the utilization by the tissues, was the same in the depancreatized state as in the normal. This, however, is only claimed within the limits of a period of six hours after depancreatization. Further experiments upon the effect of time will be undertaken.

It may be argued that six hours is not sufficient time to allow for an interference of oxygen to take place, and that while the pancreas may have been removed, its internal secretion was still present in the blood controlling the oxidation of glucose. If such be argued we must then admit that hyperglycemia and glycosuria are phases of the diabetic state independently of oxidation in the tissues. In the above experiments a hyperglycemia and glycosuria were produced by the removal of the pancreas, while the oxidation remained normal.

The hyperglycemia of the diabetic state receives no satisfactory explanation upon the theory of underoxidation unless a full storage of glycogen is present. In the body glucose is rapidly converted into glycogen until finally there is reached a condition of equilibrium represented by the equation:

$$\text{Glucose} \rightleftarrows \text{Glycogen}$$

In such an equilibrium should the glucose increase, the quantity of glycogen must also increase. But in the diabetic state there is little or no glycogen present. This is the very opposite from that which we would be led to expect from the mass reaction of glucose to glycogen.

Without a full storage of glycogen through the tissues the underoxidation can not satisfactorily explain the hyperglycemia. Many observers have found that the diabetic liver does not store glycogen. Minkowski[4] observed that depancreatized dogs had no storage of glycogen in their livers. It has been confirmed by many others. Epstein and Baehr,[5] Claude Bernard,[6] Naunyn,[7] Lepine,[8] Demyer,[9] and Hedon.[10] Another explanation of the hyperglycemia with its glycosuria than that given by underoxidation is necessary.

The hyperglycemia is readily explained if we assume glycogenic function for the pancreas. This theory of the nature of the function of the internal secretion of the pancreas is supported embryologically as well as experimentally. In general it is believed that the "islands of Langerhans" are the gland cells of the internal secretion. Embryologically they arise from the intestinal tract associated with a gland which has an external secretion that hydrolyzes the starches, and remain associated with this gland. The development of the islands is intimately related to the development of the acini. It is logical to conceive them from their development and position as modification of the acini of this gland.

This is not a functional modification, but a structural one, in order that the secretion may be diverted into the portal blood to act as synthetic enzyme while the external passing out through the duct is a hydrolyzing enzyme. This hydrolysis or splitting of starches into glucose may be represented as follows:

$$\text{Starch} + \text{Enzyme} \rightleftarrows \text{Glucose} + \text{Enzyme}.$$

The splitting of the starch proceeds until there is a certain ratio of glucose to starch or until a certain equilibrium is reached. If, however, the glucose is removed from the field of reaction as in the body by diffusion through the wall of the intestinal tract, the entire amount of starch is hydrolyzed. The enzyme does not change the nature of a reaction, but only its velocity, which it increases.

If we now conceive that the internal secretion poured into the portal blood stream from the structurally modified islands has the same function as the external

secretion, we are able to follow the fate of the glucose after it reaches the portal circulation. As the glucose diffuses through the intestinal wall and into the portal blood it is met by the internal secretion. Since it is entirely glucose the reaction becomes synthetic and the enzyme gives the needed velocity. The reaction will be:

$$\text{Glucose} + \text{Enzyme} \rightleftarrows \text{Glycogen} + \text{Enzyme}.$$

As the glycogen passes through the liver it is removed from the blood. This may be represented diagrammatically (Fig. 1). Conversely if the internal secretion does not reach the portal system a slow and inefficient synthesis with consequent hyperglycemia and glycosuria will result. When it is realized that at most there is only three to five grams of glucose in the blood and a hundred grams will be absorbed in an hour the need of swift synthesis into glycogen is seen.

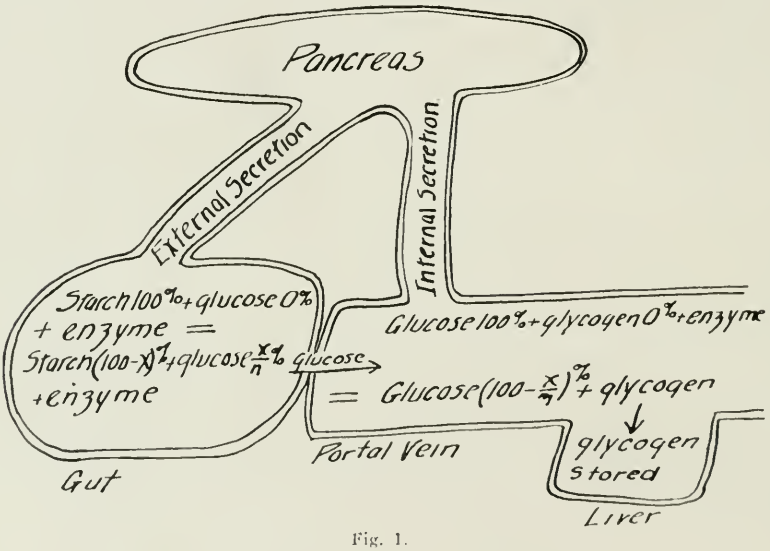

Fig. 1.

Here then, if we can prove the glycogenic function of the internal secretion of the pancreas, we find an explanation of the hyperglycemia and corresponding absence of glycogen. In addition I expect in subsequent articles to show that this absence of glycogen in itself is sufficient to explain the fatty changes, the acetone bodies, the disturbed respiratory quotient, and the failure of a carbohydrate diet to raise the respiratory quotient or check the acetonuria in the state of pancreatic diabetes.

ANIMAL EXPERIMENTS UPON THE GLYCOGENIC FUNCTION OF THE PANCREAS

Experiment 1.—A rabbit (2,000 grams), starved for eight days, was put under ether and its abdomen opened. Sample 1 of blood was taken from left side of heart with syringe. The pancreatic vein was then clamped and Sample 2 taken from left side of heart. The vein was then unclamped and an interval of ten minutes allowed. Glucose solution (20 c.c. of 18 per cent) was then injected into the ileum. In five minutes Sample 3 was taken from left side of heart. Again the vein was clamped and after five minutes Sample 4 was taken from left side of heart.

The Analysis of Samples

Sample 1.—Blood sugar, before clamping pancreatic vein	0.176%
Sample 2.—Blood sugar, after clamping pancreatic vein	0.175%
Sample 3.—Blood sugar, with glucose in gut	0.208%
Sample 4.—Blood sugar, pancreatic vein clamped with glucose in gut	0.308%

The clamping of the pancreatic vein prevented the removal of the glucose from the blood. The sugar concentration did not rise when there was no glucose in the gut and the vein of the pancreas was clamped. When the glucose was placed in the gut and the vein free the concentration rose 0.033%. But when the vein was clamped with the glucose in the gut the concentration in five minutes rose 0.100% about three times as rapidly. (Chart 1, Curve 1.)

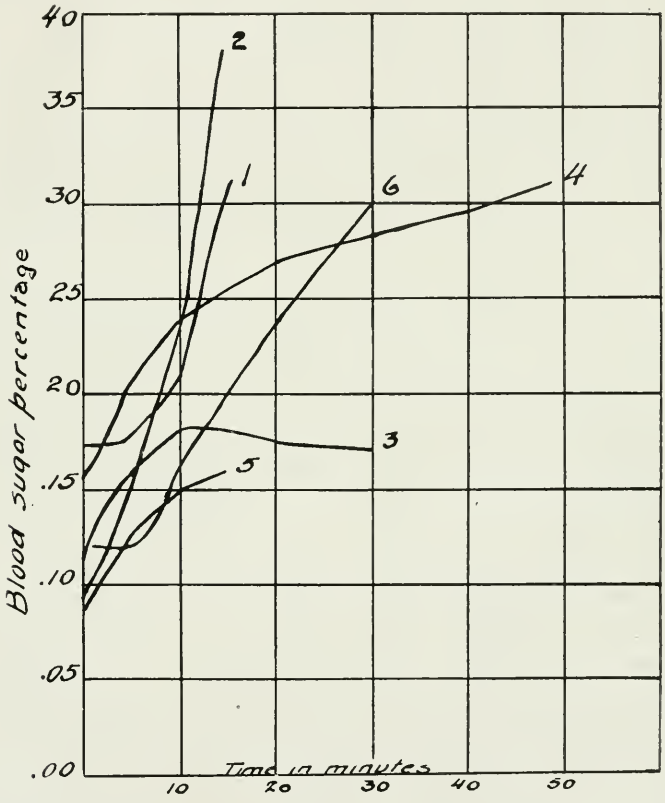

Chart 1.

Experiment 2.—A rabbit was put under ether and the abdomen opened. Blood Sample 1 was taken from the left side of heart. A glucose solution (20 c.c. of 18 per cent) was injected into the ileum. Ten minutes later Sample 2 was taken from left side of heart. The pancreas was then totally removed. After five minutes Sample 3 was taken from left side of heart. One c.c. of urine was found in the bladder and removed. It reduced Fehling's solution. The analysis gave the following (Chart 1, Curve 2):

Sample 1.—At beginning of experiment	0.094%
Sample 2.—After injection of glucose in gut	0.200%
Sample 3.—After removal of pancreas	0.386%

A hyperglycemia resulted.

Experiment 3.—A rabbit (1,900 grams) was put under ether. Blood samples were all taken from left side of heart. Sample 1 was taken five minutes after animal was under anesthetic. The remaining samples were taken as indicated below, after the injection of 19 c.c. of 10 per cent solution of glucose into ileum.

Sample 1.—At beginning	0.118%
Sample 2.—Five minutes after glucose was in gut	0.159%
Sample 3.—Ten minutes after glucose was in gut	0.174%
Sample 4.—Twenty minutes after glucose was in gut	0.168%
Sample 5.—Thirty minutes after glucose was in gut	0.165%

Experiment 3 gives the rise in the normal. An absorption of two grams per kilo in the normal rabbit gave a rise of sugar in the blood of only 0.056 per cent (Chart 1, Curve 3).

Experiment 4.—A rabbit (1,900 grams) was put under ether and the pancreas removed. Eighteen c.c. of 10 per cent glucose was injected into the ileum. Blood samples from left side of heart were taken as indicated below.

Sample 1.—Just before injection of glucose	0.165%
Sample 2.—Five minutes after injection of glucose	0.198%
Sample 3.—Ten minutes after injection of glucose	0.240%
Sample 4.—Twenty minutes after injection of glucose	0.265%
Sample 5.—Thirty minutes after injection of glucose	0.280%
Sample 6.—Forty minutes after injection of glucose	0.295%
Sample 7.—Fifty minutes after injection of glucose	0.305%

Urine at end of experiment reduced Fehling's solution. The total rise was 0.140 per cent. A hyperglycemia developed with its related glycosuria (Chart 1, Curve 4).

Experiment 5.—A rabbit (2,000 grams) was put under ether—20 c.c. of 10 per cent glucose injected into ileum. The blood samples from left side of heart were taken as given below (Chart 1, Curve 5):

Sample 1.—Immediately after injection of glucose	0.090%
Sample 2.—Five minutes after injection of glucose	0.130%
Sample 3.—Fifteen minutes after injection of glucose	0.150%

Again the rise in the non-depancreatized animal was insignificant.

Experiment 6.—Rabbit, weight 1,800 grams, was put under ether. All blood samples were taken from left side of heart at times indicated below. A solution of glucose was injected into ileum and the pancreas removed. Glucose analysis of blood.

Sample 1.—Before pancreas was removed	0.122%
Sample 2.—Five minutes after removal of pancreas	0.115%
Sample 3.—Ten minutes after removal of pancreas	0.156%
Sample 4.—Twenty minutes after removal of pancreas	0.237%
Sample 5.—Thirty minutes after removal of pancreas	0.300%

Here as in the other experiments when the pancreas is removed the rise of glucose is rapid and high.

In all of these animal experiments the rise of percentage of blood sugar when 2 grams of glucose per kilo was given through the intestinal tract varies widely according to whether the animal is normal or depancreatized.

In the above experiments we find two different conditions of the percentage of sugar in the blood. In the normal animal we find that 2 grams of glucose per kilo does not produce a severe rise in the percentage in the blood, but in the depancreatized animal the rise is quick and severe enough to bring about a glycosuria. In the normal animal the glucose diffusing into the portal blood is met by the internal secretion of the pancreas and rapidly converted into glycogen. The rate of conversion is such as to prevent a hyperglycemia of such proportion as

to produce a glycosuria. But in the depancreatized animal the conversion does not take place and a hyperglycemia and glycosuria results. The hyperglycemia is due to the lack of the internal secretion of the pancreas.

With this fact we are in a position to discuss the rate of absorption of glucose from the intestinal tract and the rate of its conversion into glycogen, to the rise in concentration of the blood sugar. It is this relation that is altered in the state of pancreatic diabetes. In the normal individual the rate of hydrolysis of starch and its absorption as glucose is below the rate of the conversion of the glucose into glycogen. When this is changed and the rate of conversion of the glu-

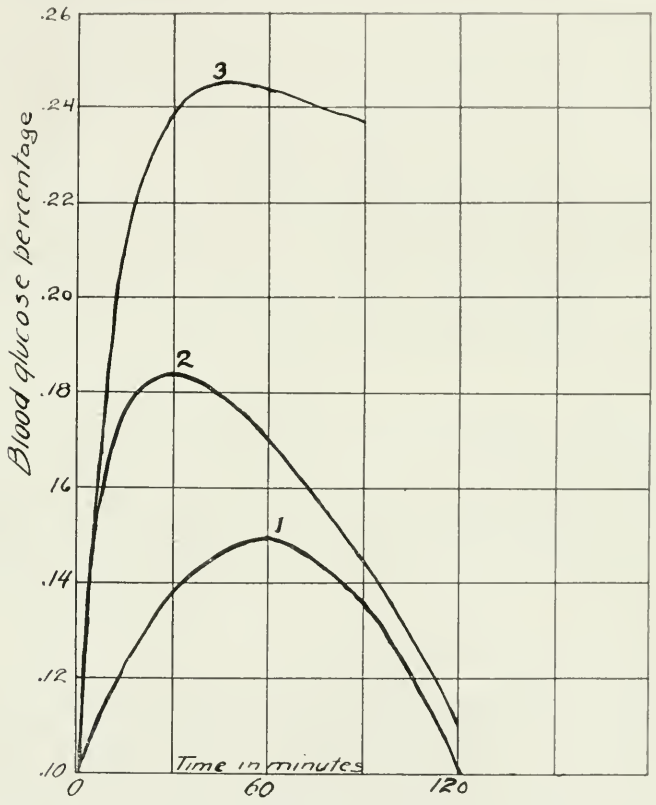

Chart 2.

cose to glycogen becomes less than the rate of the absorption of glucose from hydrolysis of starch, the blood sugar rises, there is a hyperglycemia, and glycosuria develops. The enzyme for the rapid conversion is the internal secretion of the pancreas. The rate of absorption of ingested glucose is different. An individual in normal condition will upon the ingestion of one hundred grams of glucose show a rise in the concentration of the blood sugar of 0.040 per cent to 0.050 per cent in an hour. At the end of the second hour the blood is again normal. Curve 1, Chart 2 shows the curve of a normal individual upon 100 grams of glucose. A hundred grams of glucose given per mouth does not produce a hyperglycemia high enough to give a glycosuria, because it is too rapidly converted into glycogen. In the diabetic state where the internal secretion of the pancreas is at fault the con-

version of glucose into glycogen is too slow and hyperglycemia of severity is the result. This slow conversion of glucose into glycogen is the state of diabetes.

Again in Chart 2, Curves 2 and 3 are the curves of a diabetic. Curve 3 gives the rise of the blood sugar upon feeding a hundred grams of glucose. In this case the blood sugar rose from 0.10 per cent to 0.240 per cent in one hour. At about 0.18 per cent glycosuria becomes noticeable. The rate of rise in the diabetic is very much greater than in the normal. Curve 2 is the same patient upon 30 grams of glucose. The rise is almost as rapid as shown in Curve 3 yet at the end of half an hour has reached its crest and at the end of two hours had returned to normal. The difference between these curves is not because of oxidation, but because of the change in the rate of conversion into glycogen and its storage. The condition represented by Curves 2 and 3 is exactly the same condition we found in the depancreatized animals. When the animal is depancreatized it is no longer able to convert the absorbed glucose into glycogen, no glycogen is stored and a hyperglycemia with glycosuria develops; the diabetic through a disease of the pancreas in a similar way loses the internal secretion, fails to convert glucose into glycogen—and to the degree that he lacks this internal secretion he develops a hyperglycemia and glycosuria. If we estimate the consumption of glucose per hour as 15 grams in a resting individual (360 grams per day) and feed this to a diabetic we should expect to see the curve of the blood sugar return to normal at the end of the hour. This is what happens as shown in Curve 2, Chart 2.

Not only in the depancreatized animal, but also in the diabetic person, the external secretion of the pancreas acts as a synthetic enzyme upon the absorbed glucose. When the pancreas is functioning, the person converts his glucose into glycogen at a rate sufficient to prevent a severe rise in his blood sugar; when it is not functioning, he is unable to convert the glucose at a sufficient rate and the percentage of glucose in the blood rises, giving a hyperglycemia and glycosuria.

SUMMARY

The experiments show that a depancreatized animal as long as six hours after depancreatization develops a hyperglycemia and glycosuria just as in the true state of pancreatic diabetes, yet consumes glucose at the same rate as the normal animal. The hyperglycemia and glycosuria are dependent upon the rate of synthesis of glucose into glycogen and not upon interference with the normal rate of oxidation.

We believe that the internal secretion of the pancreas is an enzyme, similar to the external, but diverted into the portal blood for the rapid synthesis of glucose into glycogen.

The failure of its action is the cause of the state of pancreatic diabetes; a diabetic is one who fails to synthetize the absorbed glucose into glycogen at a sufficiently rapid rate to prevent a hyperglycemia.

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STUDIES ON CHOLESTEROL*

VI. The Value of Blood Cholesterol Determinations and Their Place in Cancer Research

By Georgine Luden, M.D., Rochester, Minn.

THE cholesterol content of the blood has been studied thus far mainly for the purpose of scientific investigation, and its clinical significance has received but little attention. With the exception of Joslin, Rothschild, and perhaps a few others, clinicians seem to be under the impression that cholesterol determinations have little or no practical value.[7, 8]

The observations I was able to make between November, 1915, and November, 1918, strongly suggest, however, that the test for cholesterol is capable of giving valuable clinical information, although it should not be looked upon as a specific, diagnostic test, such, for example, as the Wassermann test. It might fitly be compared to the test for albumin in the urine, the clinical value of which is beyond dispute, even though the latter does not enable us to differentiate between cystitis and nephritis without other data.

Rothschild has pointed out that in cholelithiasis the absence of a constant hypercholesteremia is due chiefly to the rate of precipitation of the cholesterol in the gall bladder, hence low blood cholesterol values would naturally occur if the surplus cholesterol had been used up in the making of the gallstones, while high blood cholesterol values associated with gall bladder symptoms, in the absence of stones, might merely indicate that the gallstones had not had time to form; that continued hypercholesteremia is well calculated to lead to the formation of gallstones is self-evident.

We are still in the dark concerning the chemical factors which cause the bile-cholesterol to crystallize to gallstones around a nucleus of bacteria and desquamated cells in some cases, while in others no gallstones are formed, although both bacteria and cell detritus are present. Rosenow obtained cultures of pathogenic bacteria (streptococci, bacilli Welchi, colon, typhoid bacillus, etc.) from the core of ordinary mixed gallstones in 29 of 34 experiments, but found no pathogenic bacteria in 4 pure cholesterol stones. The latter are obviously formed by a more rapid type of precipitation, although we do not know the factors by which this precipitation is brought about. We know, on the other hand, that "typhoid-carriers" may harbor typhoid bacilli in their gall bladders for

*From the Mayo Foundation, Rochester, Minn.

many years without being afflicted with cholelithiasis. Since the cholesterol content of the bile must be influenced by the cholesterol content of the blood, the study of the latter is eminently fitted to furnish data concerning the cholesterol metabolism resulting in the formation of gallstones.

Apart from the problems connected with cholelithiasis, the cholesterol content of the blood appears to play an important part in growth, both normal and neoplastic. Robertson and Burnett have shown that the rate of tumor-growth in rats can be materially accelerated by intravenous injections of cholesterol, but that, if the structure of the cholesterol molecule is changed (by transformation of "pure" cholesterol into acetyl-cholesterol or cholesterol chloride, that is into "changed" cholesterol) the tumors will no longer be affected. The writer[10-14] has repeatedly called attention to the importance of the blood cholesterol in connection with cell proliferation and was recently[14] able to show that radium treatment increased the amount of changed cholesterol in the blood while reducing the pure cholesterol. The mechanism of this effect of radium is still by no means clear (there seems to be some relation to the lymphocytic and leucocytic reaction), but it was observed that those patients who showed the greatest increase in difference between their pure and changed cholesterol, also appeared to derive the greatest benefit from the treatment. This observation seems specially significant in the light of Robertson and Burnett's investigations, but it is obvious that massed evidence will be required before we can hope to understand the mechanism involved in the relation between cholesterol metabolism and malignant growth. Further observations by many independent workers are therefore urgently needed. In this connection five points should be emphasized:

1. The nature of the test for cholesterol.
2. The importance of a uniform method for cholesterol determinations.
3. The source of the cholesterol intake.
4. The factors that influence the blood cholesterol.
5. The practical results to be expected in cancer research from the study of cholesterol metabolism.

Nature of the Test for Cholesterol.—Since cholesterol is a definite chemical entity and the test for cholesterol is based on purely chemical reactions, the condition under which determinations are made must control the values that are found in our determinations. In the literature dealing with the cholesterol content of human blood in health and disease, there exists at present a somewhat bewildering lack of uniformity as regards the values given by different writers. In many instances we find the most contradictory statements concerning the blood cholesterol values which accompany pathologic conditions. Such contradictory reports can undoubtedly be explained to a great extent by the varied technic used for the determinations:

1. The many methods used for the extraction of the blood cholesterol.
2. The fact that whole blood was used by some and only blood serum by others.
3. The relative strength or nature of the color standard in colorimetric determinations (it is well known that light shades can be matched more accurately than darker shades of any given color, and that the cholesterol standard and blood cholesterol generally have a slightly different tint).

4. The "setting" of the colorimeter for the standard, because of its influence on the relative depth of color of the standard solution.

5. The temperature at which the determinations were made; a relatively high temperature (35° C., suggested by Autenrieth) tends to produce lower values than does room temperature (20° to 22° C.), a fact to which I have called attention,[10] and which has since been corroborated by Bloor.[5]

6. The time during which the tests are allowed to "ripen."

7. The effect of daylight on the color reaction. Tests left in the dark assume a yellowish-green tone, whereas the same sample will be bluish-green when exposed to the light for the same length of time and at the same temperature. The color of the standard cholesterol always has a tendency to be more bluish (emerald green) than the blood sample and the respective shades can be more accurately matched if the tests correspond in tone.

Another important factor to which I also recently called attention is that there are two distinct types of blood, each with a different rate of color reaction; the rapid and the slow.[11] The rapid type reaches its color maximum ahead of the commercial cholesterol standard and fades more rapidly than the latter. The slow type reacts less quickly but retains its color maximum longer. Unless this peculiarity is duly taken into account, especially when extreme representatives of either type are being tested, the values recorded will not be in accordance with the actual cholesterol content of the sample. Jaundiced patients usually have the very slow type of blood because of the bile derivatives present in the circulation. It has not been possible thus far to determine in what conditions the very rapid type of blood is most frequent; the rapid reaction was found in a good many cases of exophthalmic goiter, but the rapidity of the cholesterol reaction did not seem proportionate to the metabolic rate of the patient. In all our cholesterol determinations special attention has been paid to the rate of reaction of the test, which might introduce an element of error. Bloor has made the same observation and states that "the blood cholesterol behaves differently from the standard cholesterol." A permanent standard, would, therefore, undoubtedly offer many advantages, and will be discussed in connection with the need of a standardized, uniform method of procedure.

The blood constituents which are responsible for the different rate of color reaction are eliminated to a greater or lesser extent according to the method used for extraction. They may be looked on in a general sense as "changed" cholesterol, and are, in part at least, closely related to various bile derivatives.[12]

Importance of a Uniform Technic in Cholesterol Determinations.—It can not be emphasized too strongly that, unless comparable results are obtained by many observers, it will be impossible to establish the relation of cholesterol metabolism to pathologic conditions. The use of different methods for clinical observations is bound to result in conflicting findings and has undoubtedly been responsible for the conclusion that cholesterol determinations are of little practical value. In biochemic studies the use of various methods offers certain advantages, but for clinical observations a uniform method of procedure would seem a *sine qua non*. If we consider the clinical data supplied by hemoglobinometry, the truth of this statement will straightway be apparent. In hemoglobin

determinations the actual color value of the blood may be influenced by the presence of other blood constituents, but the fact remains that the hemoglobin test has proved a valuable asset to the clinician.

Bloor's methods, which have been used in all our determinations, seem particularly well adapted for clinical work, as they have two advantages, first, the extraction is both simple and complete, and second, the amount of changed cholesterol can easily be determined by means of parallel determinations with the Bloor I and Bloor II methods. Since systematic observations by these methods have already furnished data of clinical interest with regard to the effect of radium on the blood cholesterol,[13] it seems highly desirable that further independent observations should be made along these lines.

A detailed outline of the technic[20] used in our cholesterol determinations will be given in the hope that it may be of use to others working with cholesterol. The outline contains suggestions concerning a number of "pitfalls" to be found in cholesterol determinations, which we learned to recognize while determining the cholesterol content of more than 1500 individual blood samples. (See Tables I and II.)

The Source of Cholesterol Intake.—Cholesterol ($C_{27}H_{45}OH$) forms a constituent of every mixed diet. Our daily food is therefore a perpetual source of cholesterol intake. To compute a diet that is entirely free from cholesterol but containing the requisite number of calories, as well as the necessary amounts of protein, carbohydrates, fat, and mineral salts, might be a difficult task. Such a diet would probably be very unpalatable and it is doubtful, to say the least, whether it would prove beneficial in the end.[13] Milk, eggs, and butter for instance, which even when we do not use them in pure form, are yet to be found associated with most of our food when it is ready for consumption, would have to be eliminated completely. Table III shows clearly, however, that certain foodstuffs contain far more cholesterol than others.

Whether the body possesses the power of synthesizing cholesterol from cholesterol-free material is still a matter of dispute. Oatmeal contains no cholesterol, yet when a considerable amount of oatmeal is consumed the blood cholesterol values are markedly increased. This paradoxical phenomenon is still unexplained and so far as I know, we have no means at our command by which the problem can be solved, though tentative explanations have been suggested in Studies on Cholesterol IV.[13]

Since cholesterol metabolism appears to be a factor in malignant conditions, however, the cholesterol intake in our food would seem to deserve more attention than it has hitherto received. We know that in diabetes the metabolism of the carbohydrates is impaired and that the pancreas of the diabetic is less efficient than the normal pancreas. Joslin has shown that the treatment of diabetes constitutes one of the triumphs of modern medicine. By eliminating or restricting the use of the foodstuffs that the diabetic can not "handle," patients may be kept well and happy. Joslin gives the history of a man (Case 629, p. 559)[9] whose condition was complicated by tuberculosis and angina pectoris when he came under observation in 1913, but "who still leads an active life at the age of seventy-eight years, and has lately taken up politics." This patient had, however, been kept "under close supervision by a devoted nurse, thoroughly trained

in diabetes." If so much can be done for diabetics by safeguarding the weak spot in their metabolism, it seems rational at least to try to lighten the task of cholesterol metabolism for cancer patients by advising them to avoid foods that are rich in cholesterol.* The cholesterol content of the blood can be increased, even in a healthy person by the consumption of a great deal of meat (Fig. 1), and that eggs, with their high cholesterol content, are likely to have the same effect, is to be expected.

In diabetes chemical analyses supply the means by which we gauge the progress or the exacerbation of the patient's condition, but systematic observations and uniform methods had to be employed over a considerable period before prac-

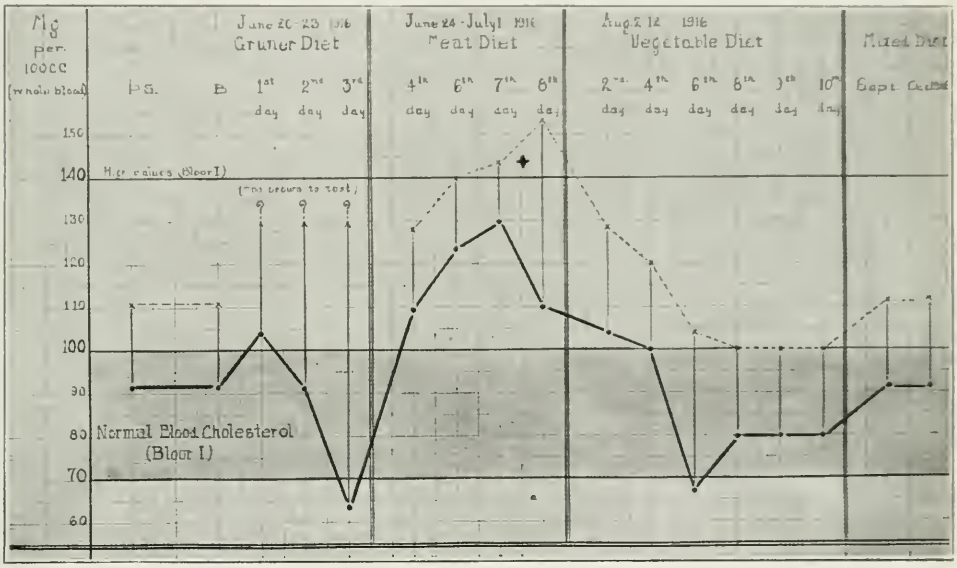

Fig. 1.—P.S: The personal cholesterol standard of the writer from January to June, 1916. The tests were made at irregular intervals and showed practically no variations. B: The test taken the day before the experiment was started.

Grunner's diet: Milk, water, bread, and lettuce. The Bloor II values could not be determined; the tests were too brown-green because of a great amount of "changed" cholesterol, as shown by the rapid drop of the Bloor I values (Bloor I solid line, Bloor II dotted line).

Meat Diet: Meat was used exclusively for every meal, except for a very small piece of bread to "help the meat down" when the latter became very repugnant. + Attack of diarrhea, increasing Bloor II and lowering Bloor I.

Vegetable diet: Vegetables and fruit exclusively, tea and coffee as usual. Observe the drop of Bloor I values, and the satisfactory amount of "changed" cholesterol during this period as well as the gradual decrease of the changed cholesterol (vertical line) during the exclusive meat diet before diarrhea intervened, and that no diarrhea occurred on the vegetable diet, but that the blood settled down to a lower level.

Mixed diet: Meat twice a day, fruit, vegetables, tea and coffee, no alcohol; the usual type of ordinary mixed diet. Observe that the blood cholesterol returns to its former level.

tical results could be obtained; many factors besides the percentage of sugar in the urine had to be taken into consideration in order to reach the therapeutic successes that we observe today.

In carcinoma systematic observations on the cholesterol content of the blood by a uniform method, and in connection with dietetic and therapeutic measures

*Here again massed evidence will be required. At my suggestion a number of patients have reduced their cholesterol intake, apparently with beneficial results, but sufficient time has not elapsed to warrant definite conclusions. Blood cholesterol determinations and complete blood counts have been made to check up the condition of these patients and the results thus far may be looked on as promising. The details of the observations will be published later. Bulkley has advocated dietetic measures for many years and has recently again emphasized the metabolic origin of cancer.

would not only help to keep us informed, but also very materially further our understanding of the causes of malignant growth.

Factors That Influence the Blood Cholesterol.—The amount of changed cholesterol present in the blood is influenced by a number of factors. It is influenced to a marked extent by radium treatment, by the process of digestion (a factor that may, however, be easily eliminated by taking the blood before breakfast), by acute bacterial infections, and apparently by ulceration and hemorrhage. This shows that cholesterol metabolism is influenced directly by any process causing a reaction in the body, that is, by a process that tends to increase the metabolic rate. In myxedema an inversely proportional relation has

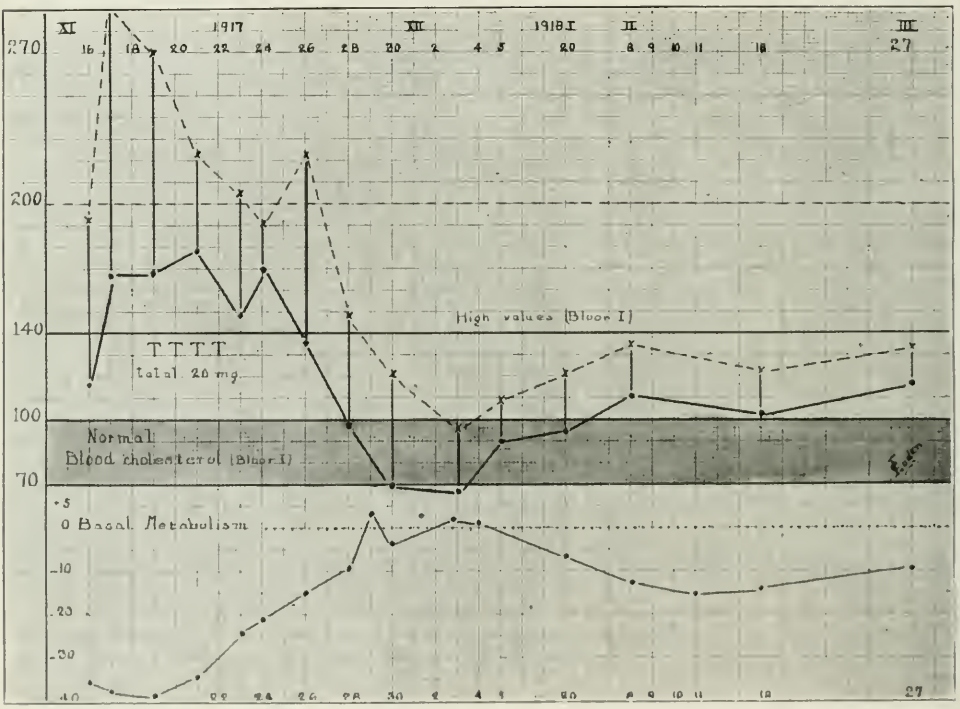

Fig. 2.—The relation between the rate of basal metabolism and the cholesterol content of the blood; observe that it is inversely proportional. The patient, a pronounced case of myxedema, went home perfectly well after the administration of the thyroid hormone (Kendall's thyroxin), 5 mg. at each dose.

been observed between the cholesterol content of the blood and the rate of basal metabolism[19] (Fig. 2). It will also be remembered that the process of spontaneous regression in malignant tumors, whether the tumors be grafted or of autogenous growth, is usually accompanied by ulceration, "sloughing" or hemorrhage; that radium treatment produces these symptoms as well as a "general reaction" in many cases; that acute bacterial infections (such as erysipelas, for instance) often exert a curative influence on the growth of tumors, and that the rate of basal metabolism is manifestly increased by all of these factors, as shown by the accompanying febrile reaction. Consequently recent bacterial infection, ulceration, sloughing and hemorrhages will have to be taken into account in the clinical interpretation of our cholesterol values. In the results obtained by Coley's treatment, the "reaction" plays a prominent part; its effect on the relation be

tween pure and changed cholesterol in the blood would therefore seem well worth investigating.

In this connection I wish to call attention to the significance of Rhodenburg's[17] analysis of 302 cases of spontaneous recession of tumor in man. For the sake of convenience Rohdenburg's Group IA is given in tabular form. This group contains 43 cases (25 of carcinoma, 10 of chorioepithelioma and 8 of sarcoma) all showing complete recession, carefully controlled. The sequence in which the cases are given in Rohdenburg's article has been observed and the different types of tumors (Tables IV, V, VI) have merely been separated. The importance of the fact that these tumors disappeared, and that a patient was well and free from recurrence for a period as long as three and a half years in a case of melanosarcoma and of twenty-two years in a case of carcinoma, can hardly be overestimated. It would seem conclusive evidence that the human body is capable of waging a successful battle against malignant disease, for, in the instances quoted, this battle was fought and won under the most untoward conditions; in some cases the tumors were inoperable and the patients were sent home to die. Their condition would have justified the most pessimistic prognosis; none of them received radium treatment, and the operations that are recorded were for the greater part either "palliative" or "incomplete." Yet tumors, as well as recurrences, disappeared and gave no more trouble.

That the stimulation of the metabolic rate played some part in these recoveries, is suggested by the following: Among the cases of sarcoma, bacterial infection intervened in 4 of 8 cases; one case of chorioepithelioma, a "febrile convalescence of six days" is especially mentioned, in another the patient "had a temperature of 41°C. (106°F) for several days." No febrile reaction is reported in the carcinoma group that showed complete recession, but the reabsorption of the tumors themselves is likely to have stimulated the metabolic rate, to a certain extent, since the reabsorption of body proteins (exudates, hemorrhage) is almost invariably accompanied by a rise of temperature and the latter indicates a rise of the metabolic rate. That a too rapid reabsorption of protein material, by overdriving the organism as a whole, may become fatal to the patient is illustrated by Case 3 in Table III. In the other instances, however, reabsorption appears to have been less precipitous, and being more gradual, might have insured a continued stimulation of the metabolic processes by which the chemical conditions in the body were effectually altered. Be this as it may, the fact remains that in apparently hopeless cases the patient became "clinically well" (which after all is the main thing from the patient's point of view) and that they did so under conditions well calculated to increase the rate of their basal metabolism.

Unfortunately we do not possess at present any data obtained by modern methods on the metabolic rate in malignant conditions. I am beginning to collect such data but thus far only two observations have been available; in both instances the metabolism proved to be somewhat below normal. Two observations do not constitute much evidence and a metabolic rate that is only slightly below normal (8 and 11 per cent) may seem insignificant, but it will be conceded that even a slightly subnormal metabolic rate, existing over a prolonged period—half a lifetime maybe—may as effectually disturb the chemical con-

ditions under which the body cells have to exist, and influence the cells more potently, than a marked derangement of metabolism covering a short period. Systematic observations on the rate of basal metabolism in carcinoma before and after radium treatment in connection with the cholesterol content of the blood and the lymphocytic reaction (Murphy's "lymphoid defense") should therefore be looked on as valuable assets in the study of the cancer problem. It is obvious, however, that investigations along these lines can not be carried out by a single person; here again massed evidence must be obtained in order to furnish conclusive data.

The Practical Results to be Expected in Cancer Research from the Study of Cholesterol Metabolism.—There can be little doubt that the functional inefficiency of one organ may become the primary cause of perverted metabolism; no matter whether that organ has become inefficient after being "damaged" in some way, or whether it was originally inferior through faulty differentiation. The influence of thyroid inefficiency on the metabolic rate in myxedema, and the inadequacy of the pancreas and the chemical derangement it produces need only be recalled.

I have previously suggested[10] that the hereditary transmission of inadequate organs may be a primary factor in the etiology of malignant disease. Since we admit the hereditary transmission of external features (the family nose, the Hapsburg lip) and prove our belief in heredity by the attention devoted to our pedigreed stock, we can not logically deny that internal organs must also be subject to hereditary transmission. But if internal organs are transmitted thus, it follows that their inability to do their work properly must also become the cause of faulty metabolism and produce abnormal chemical conditions in the body. Nor is it to be expected that the composition of the blood should be normal under these circumstances, and, since the blood is the main source of food supply for all the body cells, the abnormal chemical composition of the blood is bound to affect the life of the cells, their structure, their development and their rate of proliferation.

In carcinoma we have not yet been able to recognize the organ that may be chiefly responsible for the type of faulty metabolism that can incite the cells to lawless proliferation. In diabetes, however, we know one organ at least that is unequal to its task, the pancreas. Numerous microscopic studies have failed to reveal any striking histologic changes in the pancreas of the diabetic; the gland seems to be merely functionally inefficient. Moreover, we admit that diabetes "has a tendency to run in families" (Joslin) and thereby indorse the fact of the hereditary transmission of the inadequate gland. By systematic observations on the chemical features that characterize the disease and which are, for the greater part at least, due to pancreatic inefficiency, we are now able to prolong the life or add to the comfort of diabetics to the extent described by Joslin. Had the same amount of energy that has been devoted to the study of chemical and metabolic details in diabetes, been similarly employed in cancer research, the verdict "that 90 per cent of those in whom carcinoma develops, succumb to the disease"[6] might never have been pronounced. Neither should it be forgotten that the chemical abnormalities observed in the blood of diabetics, high alkalinity, increased sugar content, and hypercholesteremia, are also found in car-

cinoma.[14] Moreover, cancer very frequently develops in diabetics (Robin, Joslin), whereas it is said that cancer patients rarely acquire diabetes. Possibly the latter statement might have been modified, if our chemical data had been collected with equal care in both diseases.

It would be obviously unwarranted, as well as foolish, to ascribe a common origin to conditions that differ so much in their manifestations as do diabetes and carcinoma; but a fundamental similarity may nevertheless exist between them; namely, the functional inefficiency of individual organs; the dissimilarity of the organs that were primarily responsible would naturally determine the course of the diseases in either case.

The results obtained in the treatment of diabetes are sufficiently striking, however, to stimulate our efforts to discover the source of those metabolic disturbances that promote lawless cell proliferation. Blood cholesterol determinations, made systematically in conjunction with observations on the rate of basal metabolism and on other chemical constituents of the blood and urine, as well as the cytology of the blood, might reasonably be expected to further our knowledge in this direction. The study of the "lipoid" metabolism is as yet in its infancy, but its relation to carcinoma seems unquestionable in the light of Robertson and Burnett's investigations.

It is for this reason that determinations of the blood cholesterol, one of the chief blood lipoids, should have a place in cancer research.

TECHNIC

1. Extraction.—The ether-alcohol extract of the blood is prepared according to Bloor's direction, namely, 3 c.c. of blood taken from the cubital vein by means of a graduated syringe, are squirted directly into 75 c.c. of the ether-alcohol mixture, (3 parts 95 per cent alcohol to 1 part ether per 100 c.c.), well shaken to insure a fine division of the blood, just brought to the boil on the water-bath the bottle being shaken slightly all the time to prevent overheating, cooled under the tap for about five minutes, and then filtered. The bottles are filled up to 100 c.c. if the tests can be made immediately, otherwise they are merely corked, sealed with paraffin, and kept in a cool place to be filled up before the tests are to be made. This routine was adopted for the sake of greater accuracy, as the ether is bound to evaporate somewhat and thereby increase the concentration of the extract. Observations have shown that most extracts will remain unchanged for from one to six months; others, however, show variations in the relation of the changed and the pure cholesterol, due presumably to a disintegration of the cholesterol molecule, so that it is safer to make the tests as soon as possible after the blood has been drawn. We do not use citrate and have not had any trouble through clotting of the blood. Sodium citrate appears to affect the cholesterol values in some types of blood (no explanation can be offered for this observation, but the matter is being investigated); we have, therefore, discarded its use in order to insure similar conditions for all our tests. The extracts are kept in graduated 100 c.c. bottles, care being taken that no increase of concentration has occurred in samples that are to be retested after weeks or months.

For the Bloor I tests, 2 c.c. of sodium ethylate (3 gm. of metallic sodium dissolved in 100 c.c. of absolute alcohol) are added to each 10 c.c. of ether-alco-

hol extract; for the Bloor II tests, no sodium ethylate is added. We use 30 c.c. of the extract for each determination, so as to have enough material for three tests in each case. The extracts are measured into beakers and evaporated to dryness on a water-bath. As soon as they are dry the samples are taken off the water-bath, to avoid overheating, and left to cool for from fifteen to twenty minutes. The residue in the beakers (a faint yellow layer in the Bloor I, but hardly visible in the Bloor II samples) is then extracted three times with small quantities of dry chloroform. Any trace of water in the chloroform interferes with the subsequent color reaction. We have found it convenient to keep the chloroform in a wide glass bottle into which has been placed a quantity of calcium chloride; the chloroform is filtered before it is used. Each 10 c.c. of the ether-alcohol extract should provide 6 c.c. of chloroform extract when the three extractions have been added together, a total of 18 c.c. of chloroform extract being obtained when 30 c.c. of ether-alcohol extract is used per sample as in our determinations.

2. Color Reaction.—To 6 c.c.* of the chloroform extract are added 2 c.c. of acetic acid anhydrid and 0.2 c.c. of water-free concentrated sulphuric acid. We use ordinary test tubes, and shake the chloroform and reagents well to insure thorough mixing. We have found that the use of 0.2 c.c. instead of 0.1 c.c. as generally recommended, has the advantage of producing a tone of green that can be matched more readily, but does not influence the cholesterol values (the same amounts of the reagents are, of course, added to the cholesterol standard). Since the color reaction is due to oxidation, it seemed possible that the use of more sulphuric acid might increase the amount of changed cholesterol. This, however, is not the case. On the contrary, in a series of some 20 samples tested both with 0.1 and with 0.2 c.c. of sulphuric the amount of changed cholesterol was slightly higher with only 0.1 c.c. in some cases, though it was not altered in the majority of them. This observation is important, because in a series of determinations of the blood cholesterol in carcinoma of the cervix before radium treatment we had found, much to our surprise, that the number of patients whose blood gave equal values with the Bloor I and II tests was very small, whereas in the series previously reported,[13] including diverse localization of the disease, the percentage of equal values had been high (56 per cent). Since the use of more sulphuric acid lessens the changed cholesterol but certainly does not increase it, the behavior of the blood in carcinoma of the cervix (namely, the relatively big amounts of changed cholesterol) can not be due to our technic, but must be due to other factors. As most of the patients suffering from carcinoma of the cervix had a history of severe hemorrhage or of ulceration, these two factors would seem to influence the amount of changed cholesterol in the blood.

3. Technic Used in the Test.—After the reagents are added, the test tubes are left exposed to the light at room temperature (20° to 23° C.) for five minutes; this enables us to watch the rapidity of the color reaction as compared with the standard cholesterol and helps us to decide whether the blood sample is of the slow or of the rapid type. It also causes the tests to assume a tint of green that is more easily matched. After five minutes the tests are poured from the test tubes into the colorimeter containers. Colorimetric readings are made at a few

* 6 c.c. tests were originally recommended by Bloor. We are using them as this greater volume is more satisfactory in the large Duboscq colorimeter, the plungers do not get out of their depth in samples containing little cholesterol.

minutes' interval from 5 to 15 minutes after the reagents are added. The reading which persists at least four times is recorded as the maximum value. The cholesterol standard begins to fade in about twenty minutes[12] and for this reason we never use a standard that is more than fifteen minutes old. The reagents should be added to the standard and to the sample as nearly simultaneously as possible, and a fresh standard should be used for each sample. Table I has been found a great convenience in our determinations, as it gives the cholesterol values in milligrams per 100 c.c. directly from the colorimetric reading.

4. Permanent Standard Solution "NBM."—Lately we have made observations with a permanent standard, the color value of which corresponds with the cholesterol standard given in Table I. This standard solution and the pure Naphthol Green B Solution recommended by Gorham and Myers can only be called "permanent" in a restricted sense; the solution itself will keep unchanged in the bottle, even when exposed to light, but the portion of it used in the colorimeter and thereby exposed to fumes of the reagents, changes its tone and decreases in color value. This is especially true if the closed Kober colorimeter is employed. Those who work with the latter instrument will have observed that a strong odor of acetic anhydride is retained in the instrument for some time after the tests have been taken out. As our containers and plungers were cleaned with special care and washed, first in a strong solution of sodium bicarbonate, then repeatedly with distilled water to remove all trace of acid, actual contact with acid can not be responsible for this deterioration of the Naphthol Green B, or of the NBM standard solution, which will, of course, result in inaccurate readings if the standard is looked on as truly permanent. We have found, however, that satisfactory and reliable results are obtained if the standard solution is renewed after each two or three samples have been tested. As in all our observations parallel determinations are made with two colorimeters, a standard cholesterol solution being used in one of them, while the reliability of the aqueous standards was being checked up, it was, of course, relatively easy to discover when the aqueous solution began to "go off." For those who only use one colorimeter, we would recommend changing the aqueous standard fairly often to insure the greatest accuracy. Even so the use of the aqueous standard will be found to be both convenient and economical. The NBM standard solution has a decided advantage in our estimation when compared with the pure Naphthol Green B, inasmuch as the latter is yellow green in tone and is much more difficult to match to the more bluish green of many of the blood samples, especially if the tests are left exposed to the light during the process of ripening as I have recommended.

Formula of the NBM Standard Solution.—NB stock solution; Naphthol Green B, 0.5 gm. to 100 c.c. of distilled water (0.5 per cent solution); M stock solution; methyl blue, 60 mg. to 100 c.c. of distilled water (0.06 per cent solution).* NBM standard solution: 1 c.c. of NB stock solution and 1 c.c. of M stock solution to 200 c.c. of distilled water. Stock solution NB should be added first to the 200 c.c. of distilled water, well stirred or shaken, after which stock solution M is added; if both stock solutions are mixed before dilution a

*Our Stock Solutions were made up in December, 1917, and have been found to be unchanged by testing them at intervals of several months against pure cholesterol standards up to the present, January, 1919. They have been exposed to the light all the time.

precipitate is apt to form which can be prevented if the naphthol green is diluted before the methyl blue is added.

In Table II a series of tests is shown which were made to ascertain the reliability of the NBM standard. If we consider that the figures given in Table II represent independent readings by three observers, and that the reaction for cholesterol is a progressive reaction in which the color formation may be slightly more rapid in some blood samples than in others (although no "very slow" specimens are included in this series) the element of error in the readings is very small, on an average of 3 mg. per 100 c.c.

The fact should be taken into account that some 1500 individual blood samples have thus far been tested by me and my two helpers, which represents a total of between eighty and ninety thousand readings, six tests being used for each sample and about ten readings for each test; consequently the opportunity to train our color vision has not been lacking.

SUMMARY

1. The test for cholesterol is not a diagnostic test, but furnishes information concerning cholesterol metabolism; it will therefore furnish information about the disturbances of cholesterol metabolism connected with cholelithiasis and carcinoma, for instance.

2. Cholesterol metabolism is influenced by the rate of basal metabolism; it was found to be inversely proportional to the latter in myxedema.

3. The reaction for cholesterol is a purely chemical reaction; technical procedures play a prominent part in the results obtained. Consequently the method of extraction and the conditions under which the color reaction takes place determine the values found in blood cholesterol determinations.

4. In clinical work, intended to promote our knowledge concerning the relation between the cholesterol content of the blood and pathologic conditions, a uniform method of procedure should be adopted for cholesterol determinations, since this alone will insure comparable findings. A detailed account of the technic used in our determinations is given, because this technic is based on the determination of more than 1500 individual blood samples, which enabled us to recognize and eliminate many elements of error in the course of our work.

5. The cholesterol content of the blood is influenced by a number of factors, the nature of the diet, the rate of basal metabolism, radium treatment, bacterial infection (ulceration, infectious disease), and hemorrhage. These factors should be duly considered in the clinical interpretation of blood cholesterol values. The cholesterol content of the blood is intimately related to lipoid metabolism and the blood cholesterol can be influenced by dietetic measures.

6. It is known that the inefficiency of an individual organ can give rise to a particular type of metabolic disturbance; inefficiency of the thyroid results in myxedema, pancreatic inefficiency in diabetes.

7. There can be little doubt that an intimate relation exists between disturbances of the cholesterol metabolism and the lawless proliferation of cells that we observe in carcinoma, although the organ that is initially responsible for these disturbances has not yet been recognized.

8. The results obtained in the treatment of diabetes show what can be achieved in the face of organic inefficiency, and these results have been obtained

by means of chemical investigations and by dietetic measures calculated to counterbalance the inefficiency of the pancreas, whereas the histologic study of the latter did not materially advance our knowledge in the treatment of the disease.

9. The fact that in a number of carefully controlled cases, the tumors receded and the patients became "clinically well," although their condition had been pronounced "hopeless," constitutes proof positive that the human body can wage a successful battle against malignant disease.

TABLE I

CHART FOR BLOOD CHOLESTEROL DETERMINATIONS

GIVING THE CHOLESTEROL VALUE IN MG. PER 100 C.C. DIRECTLY FROM THE COLORIMETRIC READING

Standard: 0.4 mg. cholesterol to 6 c.c. of chloroform.* (This concentration harmonizes best in color with the value found in human blood). The NBM permanent standard is equally satisfactory (for formula see text).

Set at: 10. mm.—**Colorimeter:** Duboscq and Kober.

Cholesterol values in mg. per 100 c.c. of whole blood

mm.	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.	17.	18.	19.	20.
	1332	666	440	333	267	222	191	167	148	133	121	111	102	95	89	83	78	74	70	67
mm.	mg.	mg.								mg									L. N.	
0.1	1210	636	430	326	261	218	188	164	146	132	120	110	102	95	89	83				
0.2	1110	603	417	318	259	216	186	163	145	131	118	109	101	94	88	82				
0.3	1020	580	410	310	251	212	183	162	144	129	117	108	**100**	93	88	82	77	73	69	66
													H. N.							
0.4	950	555	392	304	249	208	180	159	142	128	117	107	99	93	87	81				
0.5	895	533	380	296	241	204	177	157	**140**	127	116	107	99	93	87	81	76	72	68	65
									high											
0.6	840	515	370	290	238	202	175	156	138	126	115	106	98	92	86	80				
0.7	785	495	360	284	234	**200**	173	154	136	125	114	105	98	91	85	80	75			
					except															
0.8	745	477	352	278	230	198	171	152	136	124	113	104	97	91	85	79				
0.9	705	460	341	272	226	194	169	150	135	123	112	103	96	90	84	79	74	72	67	76
	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.

mm.	21.	22.	23.	24.	25.	26.	27.	28.	29.	30.
	63	60	58	55	53	51	49	48	46	44
0.5	61	59	57	54	52	50	48	47	45	43
	mg.									mg.

Values below 63 mg.: rare in human blood but usually found in goat's blood.

mm.	40.	45.	50.	60.	70.	80.
	33	30	27	21	19	17
	mg.					mg.

These values do not occur in blood but were used in color determinations of "bile derivatives."

The designation of "normal" (70-100 mg. per 100 c.c. of **whole** blood) is based on the use of The Bloor I. Method, with the "standard" and setting of the colorimeter indicated above. Values between 100-140 mg. usually were found to occur in inflammatory conditions (digestion of course being excluded for every test): we refer to them as "increased."

Values between 140-200 are referred to as "high" values with the Bloor I. Method. Values over 200 mg. were only observed in a few cases so far (3 cases of myxedema, one Ca) they have therefore been called "exceptional" in our determinations.

In carcinoma "high" values are the usual finding, though "increased" and (rarely) normal values have been observed. "Equal values," viz., identical with the Bloor I. and II. method were found in 56 per cent of the cases of carcinoma who were to have radium treatment.

After Radium treatment the **Bloor I. values** were found to **drop,** whereas the **Bloor II. values increased,** causing the "equal values" to disappear. **No** "equal values" have been found so far in **non-**malignant cases.

N. B.—It should be remembered that the **cholesterol test** is **not a diagnostic test;** it is merely a "clinical" test, like the test for albumen in the urine.

*Stock Solution (A) = 200 mg. of cholesterol in 100 c.c. of pure chloroform.
Standard " (B) = 10 c.c. of A made up to 150 c.c. with pure chloroform.

10. Investigations tending to elucidate the factors that connect lipoid metabolism with malignant proliferation, may enable us to do as much for cancer patients in the future as we can already do for diabetics. Massed evidence collected by means of uniform procedures will be needed to attain this end. Blood cholesterol determinations are a means by which our knowledge concerning lipoid metabolism can be increased; hence they deserve a place in cancer research.

TABLE II

TESTS MADE WITH NBM PERMANENT STANDARD

1. "Standardizing" of the Duboscq and Kober colorimeter against each other with ordinary cholesterol standard.
   One side of the colorimeter is used exclusively for the standard and marked S.
   Double samples of the standard cholesterol are prepared and one of these is used as "unknown," in both the Duboscq and Kober.
   Standard set at 10 mm., "unknown" reads 10 mm., 3 times by three observers.
   This shows that both Kober and Duboscq give identical readings.
2. Duboscq: Cholesterol standard 5 to 10 minutes old, set at 10 mm.
   NBM used as "unknown."
   Readings: 10.1 mm. 10. mm. 10.; 9.9 mm. 10. mm. 10.1; 10.1 mm. 10 mm. 10. mm. = 133 mg. 132 mg. 135 mg. 133 mg. 132 mg. 133 mg.
3. Kober: Procedure as above, readings vary within same limits, between three observers.
4. Kober: NBM standard set at 10 mm.
   blood sample as "unknown."

Sample A	Duboscq: Cholesterol standard at 10 mm. blood sample used as "unknown."
Bloor I 20 mm. 20 mm. 19.9 mm. 19.9 mm. 67 mg. 67 mg.	.....19.9 mm. 19.9 mm. 19.9 mm. 20 mm. = 67 mg. 67 mg.
Bloor II 11.3 mm. 11. mm. 11.1 mm. 11. mm. 117 mg. 121 mg. 120 mg. 121 mg.	.....11. mm. 11.2 mm. 11. mm. 11. mm. = 121 mg. 118 mg. 121 mg. 121 mg.
Sample B	
Bloor II 9.2 mm. 8.2 mm. 8.8 mm. 8.8 mm. 145 mg. 152 mg. 152 mg. 152 mg.	.....8.1 mm. 8.8 mm. 8.7 mm. 8.8 mm. = 164 mg. 152 mg. 154 mg. 152 mg.
Sample C	
Bloor I 11.7 mm. 11.7 mm. 11.7 mm. 11.7 mm. 114 mg. 114 mg. 114 mg. 114 mg.	.....12 mm. 11.9 mm. 11.9 mm. 12 mm. = 111 mg. 112 mg. 112 mg. 111 mg.
Bloor II 9. mm. 8.9 mm. 8.8 mm. 8.9 mm. 148 mg. 154 mg. 152 mg. 150 mg.	.....9.1 mm. 8.8 mm. 9.1 mm. 8.7 mm. = 146 mg. 152 mg. 146 mg. 154 mg.
Sample D, A mixture of all the remnants of Bloor I and Bloor II tests made that morning of which the cholesterol value was naturally beyond guessing. 10 mm. 10.1 mm. 10.2 mm. 10.1 mm. 133 mg. 132 mg. 131 mg. 132 mg.	.....10 mm. 10 mm. 10.1 mm. 10 mm. 133 mg. 133 mg. 132 mg. 133 mg.

TABLE III

CHOLESTEROL VALUE OF FOOD

(Mg. Cholesterol per 100 c.c. or 100 gm.)

THREE GM. SAMPLE	METHOD	
	BLOOR I	BLOOR II
Yolk of egg (raw)	888	888
Yolk of egg (hard boiled)	888	888
Butter	157	298*
Chicken (roasted breast)	127	127
Beef (raw)	53	53
Beef (roast)	63	63
Beef (smoked, salted, dried)	60	83**
Fish, black bass	83	83
***Mushrooms (plain cooked, agaricus campestris)	140	102
Mushrooms (stewed in butter, another batch of agaricus campestris)	70	60
Cream (raw)	61	61
Milk (raw)	28	28
Oatmeal ("porridge" boiled)	0	0

*Probably due to some coloring matter, eliminated in Bloor I by sodium ethylate.

**Reddish tone of ether alcohol extract suggests coloring matter, eliminated in Bloor I by sodium ethylate.

***Mushrooms contain phytosterol, a substance allied to cholesterol, but give the green reaction with the usual reagents, the lower value with Bloor II is an unusual phenomenon, for which no explanation can be offered; probably due to the phytosterol itself.

TABLE IV

SARCOMA : 8 CASES

*GROUP IA COMPLETE RECESSION, CAREFULLY CONTROLLED

DESCRIPTION OF FIRST FINDINGS		TIME ELAPSED UNTIL SECOND FINDINGS	
Melanosarcoma back-axilla	Primary tumor involvement of axilla removed by operation	3½ years	Still free from recurrence
Round cell sarcoma, chin cervical glands	Chin, operation, recurrence in right and left cervical glands. Left cervical removed	No time given	Spontaneous recession after erysipelas of remaining nodules
Round cell sarcoma, axilla	Operation, recurrence, incomplete curetting	13 months	No recurrence, remnants of tumor disappeared after erysipelas
"Sarcoma," axilla	Many metastases; pregnancy followed by abortion	No time given	Tumors disappeared, died six weeks later
Fibrosarcoma skull	Secondary deposits, partial removal	No time given	All tumors disappeared
Round cell sarcoma of the breast	Many metastases in subcutaneous tissues	No time given	All neoplastic deposits disappeared after acute infection of lung (pneumonia?)
Lymphosarcoma behind the ear	Inoperable	No time given	Complete recession after inoculation with erysipelas

One case of melanosarcoma showed regressive changes but "changes did not progress to the degree of clinical manifestation."

*Rohdenburg, G. L.: Fluctuations in the Growth Energy of Malignant Tumors in Man, with Especial Reference to Spontaneous Recession, Jour. Cancer Research, 1918, iii, 193-225.

TABLE V

CHORIOEPITHELIOMAS.—10 CASES

*GROUP IA COMPLETE RECESSION, CAREFULLY CONTROLLED

DESCRIPTION OF FIRST FINDINGS	TIME ELAPSED UNTIL SECOND FINDINGS	
Fundus uteri perforated, bladder involvement, part of tumor attached to bladder	16 months	Patient well, no mass palpable (febrile convalescence of 6 days)
Uterine wall perforated, pelvic involvement; incomplete removal	1 year +	At autopsy no recurrence was demonstrable
Invasion of uterine muscle; curettage	1 year	Patient well
Cherry-sized tumor, posterior wall, tumor removed	10 weeks 1 year	Curetting, no abnormal histology Patient clinically well
Nodule in vagina removed, recurrence 2 weeks later, suppuration and disappearance	10 months	Patient well
Nodules in vaginal wall and uterus, 2¼ years after hydatidiform mole had been delivered; nodules removed	10 months	No evidence of recurrence
Chorioepithelioma, curetted, temperature 106 (41° C.) for several days.	29 days later	Second curetting, negative Subsequently bore two healthy children
Abortion at 7½ months, curetted Metastases shortly after. Sent home to die (case Hörman)	1 year	Tumor and metastases disappeared Subsequently normal pregnancy

In the two remaining cases no malignancy was found after curettement in serial sections of the uterus removed by hysterectomy only a short time afterwards; consequently they hardly constitute evidence of regression.

*Rohdenburg, G. L.: Fluctuations in the Growth Energy of Malignant Tumors in Man, with Especial Reference to Spontaneous Recession, Jour. Cancer Research, 1918, iii, 193-225.

Table VI

Carcinoma—25 Cases

*Group IA Complete Recession, Carefully Controlled

LOCATION OF FIRST FINDINGS	TIME ELAPSED UNTIL SUBSEQUENT FINDINGS	
Stomach; Advanced, widespread peritoneal metastases, ascites	2½ years	Autopsy, no local recurrence, metastases, and ascites absorbed
Tonsil-tongue: So extensive as to be inoperable. Not treated, mouth wash, sent home to die	18 months	No trace of original tumor
Breast: Amputation, 1904, recurrence, 1906, August (x-ray), practically moribund until December, 1906	Dec. 28, 1906	Sudden, "overnight" absorption of entire area, died three weeks later
Breast: Amputation, recurrence in scar, metatases in liver	Next few years	No treatment, recurrences disappear, subsequently "entirely recovered"
Uterus: 1 fundus, 2 cervical, all inoperative; palliative cautery, curetting	6 to 7 years	All clinically well
Breast: Amputation, 2 years after recurrence in scar, metastases uterus, inoperable	3 years	Uterus normal, nodules in scar have disappeared
Uterus: 2 cases, inoperative, palliative curetting and cautery	4 to 6 years	Clinically free from all evidences of carcinoma
Intercostal: Recurrence of breast cancer, inoperable	7 years	Completely receded, free from recurrence
Uterus: Inoperable, palliative curettement, cauterized	4 years	Well, uterus normal condition
Maxilla: Recurrence 3 months later. No treatment	3 months	Recurrence completely absorbed
Broad ligaments: Infiltrated, incomplete removal of uterus	7 years	No evidence of malignant growth
Stomach: Inoperable, metastases to mesentery (exploratory laparotomy)	9 years	Perfectly well
Uterus: Cervix, curetted, cautery	11 years	Well, no evidence of tumor
Uterus: Curettement, cautery	11 years	Well, no evidence of tumor
Uterus: Radical operation refused, epithelioma cervix	22 years	Well, no evidence of tumor
10 remaining cases no definite data as to time given, patients well		

*Rohdenburg, G. L.: Fluctuations in the Growth Energy of Malignant Tumors in Man, with Especial Reference to Spontaneous Recession, Jour. Cancer Research, 1918, iii, 193-225.

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LABORATORY METHODS

NOTES ON THE ISAACSON METHOD FOR ESTIMATING GLUCOSE*

By Elisabetta C. Pennell, M.S., Santa Barbara, Calif.

THE rapid colorimetric method for determining glucose in urine, which was published by Victor I. Isaacson† was tried out in this laboratory with unsatisfactory results. Determinations were made on two standard glucose solutions and on twelve diabetic urines, both by this colorimetric method and by Fehling's volumetric method. The results obtained are tabulated below:

SOLUTION USED	AMOUNT USED	STANDARD FOR COMPARISON	RESULT ISAACSON'S	RESULT FEHLING'S	NO.
2.5% Glucose Solution	½ c.c.	B	5.2 %	2.5 %	1
Urine M 1/20/19	1 c.c.	A	0.5 %	2.38%	2
" P 1/14/19	1 c.c.	A	0.96%	0.88%	3
" P 1/16/19	1 c.c.	A	0.58%	0.88%	4
" P 1/17/19	2 c.c.	B	1.09%	0.78%	5
" R 1/15/19	1 c.c.	B	2.46%	3.12%	6
" R 1/19/19	1 c.c.	A	0.1 %	2.98%	7
" P 1/15/19	1 c.c.	C	1.25%	0.68%	8
" P 1/19/19	1 c.c.	A	0.00%	0.58%	9
" R 1/16/19	1 c.c.	B	1.25%	1.67%	10
" D 1/20/19	3 c.c.	A	0.00	0.4 %	11
" P 1/18/19	1 c.c.	A	0.00	0.71%	12
" P 4/18/19	3 c.c.	A	0.15	0.89	13
1% glucose solution	1 c.c.	A	0.9%	0.96%	14

These figures show a startling discrepancy. The chief difficulty for any one unacquainted with this method is in deciding the amount of sample to be used, and the standard required for comparison. The author of the method states that for percentage less than one, 3 c.c of the specimen must be used. In a determination such as (11), 3 c.c. were used, but the color of the filtrate was so dark that when diluted to compare with A, the darkest of the standards, the percentage was so low that when divided by 3 the result was zero or less. With high concentration of sugar it frequently happens that in sufficiently washing the filter paper so much water was required that the resulting solution was too light to compare with any of the standards. It is difficult to judge by a qualitative test whether the percentage of sugar is 0.8 or 1.2, for instance, so that the wrong amount of urine is frequently used, and either the resulting percentage is incorrect, or a repetition of the determination is necessary. This is more time consuming than the usual volumetric methods.

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†See Journal of Laboratory and Clinical Medicine, Feb., 1918, iii, 299.

A colorimetric method in which neither the standard nor the unknown can be moved up and down, so as to compare first with lighter and then with darker color, is necessarily inaccurate. It is found that as much as 3 c.c. of water may be added to dilute the color of the unknown in this method without making any change perceptible to the eye. Another serious source of error is the necessity for covering the tube with the thumb, or a cork, to mix the contents, so that some of the color is almost always lost.

The Sahli hemoglobinometer, for instance, is an apparatus of this type, but with it no attempt is made to read closer than 5 degrees. If a colorimeter was made with one standard and one tube for the unknown which was graduated from 0.5 per cent to 9 per cent by 0.5's it might prove more successful than the one under discussion. A colorimeter of the Hellige type would seem even more feasible. The unknown in such a determination, if too dark could be diluted half, as in phenolsulphonephthalein determinations.

The determinations above reported were made with uniform care by one laboratory worker, and the solutions prepared quantitatively. The standard solutions were made of Kaulbaum's glucose.

A MODIFIED PORTABLE ARTIFICIAL RESPIRATION OUTFIT*

By John A. Higgins, Chicago, Ill.

IN REVIEWING the literature on the subject pertaining to artificial respiration machines, valves and methods of applying, a large number of articles on the subject can readily be referred. Fells,[1] Jackson[2] Hanzlik,[3] Gates,[4] Meltzer,[5] Meyer,[6] Hoyt,[7] Hall,[8] Sollmann,[9] Stewart and Rogoff,[10] Gessel and Erlanger,[11] Brodie,[12] Brunton,[13] Schafer,[14] Ludwig,[15] etc., have each endeavored to advance the subject by designing some type of an apparatus or method of procedure.

When the medical students begin to receive their training in the physiologic laboratory, pertaining to operations on the mammalian subject, they are seldom called upon to perform operations of a major character. The laboratory outline may possibly call for a dissection and ligation of the carotid artery or arteries, vagus nerve, femoral vein, sciatic nerve, the recording of blood pressure, etc., in which cases interference with voluntary respiratory movements are, as a rule, avoided. Since we can not predict, however, the ability of the student anesthetist or the susceptibility of the mammalian animal to the anesthetic administered, voluntary respiratory movements may at any period of the experiment cease to continue. In such instances, and where the heart is performing its function normally, the logical procedure would be to stop the anesthetic and apply artificial respiration.

The question involved at this period of training is whether the medical students should be allowed to familiarize themselves with an elaborate or complicated artificial respiration outfit, which they may be unable to have access to

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in their future career or whether it should be advisable to acquaint the students with a portable artificial respiration outfit that could be, with little inconvenience, had in the experimental laboratories, hospital operating room, or on the outside in general practice.

I am inclined to favor this last view, especially so with the beginning medical students. After a preliminary training on the simpler types of artificial respiration outfits or methods of procedure more elaborate or complicated outfits or methods can, of course, then be studied.

Elaborate types of artificial respiration outfits, while they may give perfect satisfaction and be very valuable within themselves, are as a rule aimed for use in the experimental laboratories, or possibly for use in an operating room. In such places electric energy or compressed air, from a power plant, is generally accessible for applying in connection with the artificial respiration outfit adopted. Unfortunately, however, suitable energy, except hand or foot power, can not be had in numerous instances. This latter view would perhaps hold general in emergency cases where resuscitation on the human is essential to retain life. Such views on this subject are perhaps already considered by a number of the laboratory instructors. Accordingly they often utilize the hand or foot bellows as best they can in cases of emergency. To make use of the hand or foot bellows independently does not, however, produce the intermittent interruptions desired. Some device or valve may then be used in connection to produce the desired effect.

Fells,[16] and Stewart and Rogoff,[10] have brought to the attention of the medical profession a valve, as previously referred to, for producing the desired interruptions. Whether Fells had in view the principles later involved in the Stewart and Rogoff type of valve, I am unable to state definitely. Fells had also, in connection with his type of valve, two side inlets. One of the inlets was to accommodate administering ether vapors in case a tracheotomy was performed, and a second smaller inlet to accommodate a rubber tube leading directly from an oxygen gas tank. Now while the Fells type of valve may be of value from an experimental point of view, I would be inclined to question whether the extra side inlets are advisable, especially where resuscitation on the human is to be applied.

Where Fells aims on performing a tracheotomy he thus limits the use of his valve to the medical profession. While Fells is perfectly justifiable in keeping such a point in view, yet it is quite possible to eliminate the larger side outlet to his valve and still be able to administer ether vapors via Woulff bottle beyond the valve. Contrary to his view, other writers advocate that the layman or first aid man should not hesitate in applying some form of artificial respiration, even in the absence of a physician, where life is involved at a critical period. This critical period rarely exceeds more than ten minutes after voluntary respiratory movements cease.

Ordinary air contains about 21 per cent oxygen, of which about one-fifth, under ordinary conditions, of the oxygen inhaled is absorbed. This would therefore seem a reason to eliminate the inflation of the lungs with pure or nearly pure oxygen, if no more oxygen is absorbed than by breathing pure air. To dispense with both side inlets from the Fells type of valve will bring us to a point

of principle resembling the Stewart and Rogoff type of valve. The Fells type of valve would still seem to offer as an advantage a sort of safety to check too much pressure accumulating in the distensible bag which is placed in the air circuit. Stewart and Rogoff offer as an advantage a sort of a thumb screw safety to prevent the possibility of excessive pressure inside the face mask, together with the valve being attached to the face mask to cut down on excessive dead space.

Feeling still that there was an opportunity to make certain modifications for the good of the subject, I have acted accordingly. These modifications were made possible by taking a Fells type of valve and cutting out the two side inlets. Add on the rubber bumper as shown at *K* Fig. 1 to eliminate friction or wear

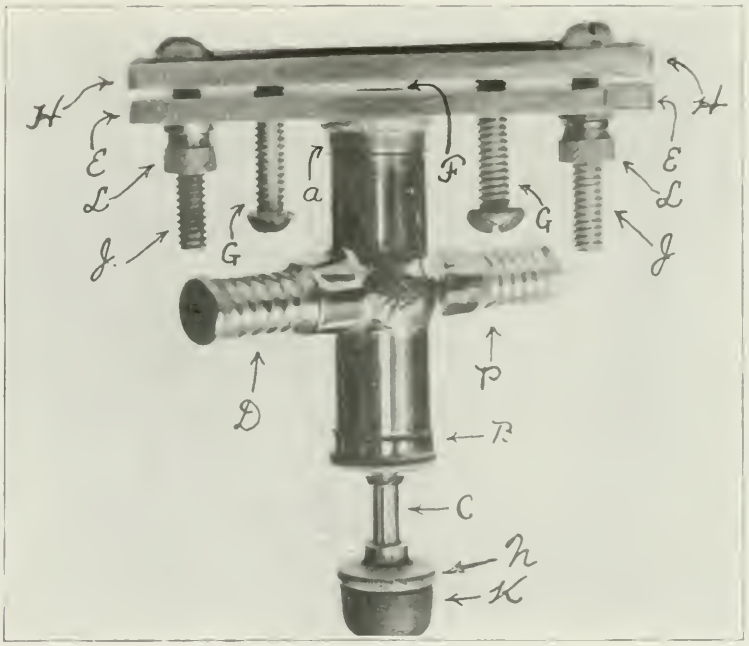

Fig. 1.—Showing view of attachment for combining with a Fletcher portable foot blower to produce an intermittent artificial respiration.

on metal piece *N*. The barrel head at *A* was then soldered to a solid piece of brass which measured $3\frac{3}{4}$ by $1\frac{1}{8}$ by $\frac{3}{16}$ inches as shown at *E*. Drill through this piece of brass, to correspond with the center of the barrel head *A*, a $\frac{3}{8}$-inch hole *F*. About $\frac{13}{16}$ of an inch, and in opposite directions from the center of the $\frac{3}{8}$-inch hole, drill two holes through the brass piece and thread them to accommodate $\frac{16}{18}$ screws *G*. These screws at *G* measure $1\frac{1}{4}$ inches over all and are used to regulate the stroke of downward movement on the foot bellows.

A second piece of metal *H*, measuring the same as piece *E*, is set flat against piece *E*. Drill a hole at each end, drilling through both pieces with a $\frac{9}{32}$-inch drill, about $\frac{3}{8}$ of an inch from the ends. These holes are to accommodate the slipping through of the $1\frac{3}{4}$-inches long by $\frac{16}{18}$-inch threaded section of the screws *J*. On the threaded section of screws *J* are lock nuts *L*. These lock nuts

are used to fasten the valve to the treadle of the foot bellows as shown in Fig. 3. The bellows here used is a Fletcher portable, number 10-B, with an 11-inch in diameter reservoir. The tubes *D* and *P* (Fig. 1) have a ⅜-inch opening and are connected to the air system as shown in Fig. 3. One of these tubes connects the outlet of the bellows reservoir to the valve. The second tube connects the valve to either a face piece or pharyngeal tube for human or a tracheal cannula, via ether vapors, in experimental mammalian work. With this outfit there is no need of any other special valve beyond the attachment itself.

The plunger used in connection is partly visible at *C*, *N* and *K*, Fig. 1, or fully visible in Fig. 2, except for the lower barrel head at *B*. The slot *E*, Fig. 2, is used in connection with an elevated section inside the valve barrel and to pre-

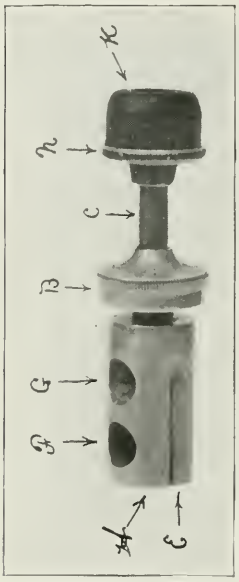

Fig. 2.—Showing view of the plunger.

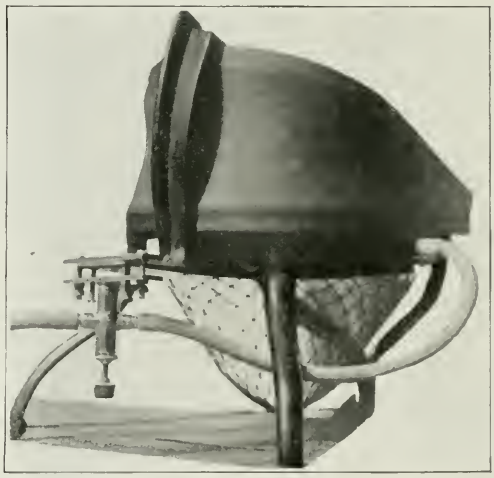

Fig. 3.—Showing view of a Fletcher portable foot blower with attachment attached and connected for producing intermittent artificial respiration.

vent rotation movements. The opening at *G* passes fully through the plunger, while the opening at *F* terminates at the end of the plunger at point *H*. A coil spring in the upper section of the valve barrel is used to keep the plunger under an outward tension.

The outfit as ready for practical use, except for the face mask or pharyngeal tube, is shown in Fig. 3. Upon forcing the bellows treadle downward, the valve being closed against air from the bellows and to the point where the lower section of the plunger hits the ground surface, the air is being transferred from the upper bellows chamber to the lower reservoir. As we continue the downward stroke, after the plunger head first hits the ground surface, the plunger is forced up into the valve barrel piece to a point where the barrel head *B* (Fig. 1) hits the shoulder *M*. When this point is reached, it brings opening *G* (Fig. 2) opposite the tube openings at *D* and *P* (Fig. 1) and thus permits the air, already placed under tension in the bellows reservoir, to proceed toward inflating the

lungs. Then upon releasing the tension from the bellows treadle the coil spring forces out the plunger to its regular position, closes the system of air from the bellows reservoir to the valve, and opens the system of air from the lungs to the outside via openings *D*, *F* (Fig. 1) and *F*, *H* (Fig. 2). This thus permits the lungs to collapse. At the same time the upper chamber of the bellows is filling up for a succeeding expiration.

It will now be noted that in this outfit I eliminate the distensible or interposed extra rubber bag between the bellows and the valve as found in other outfits. It is made possible to limit the intermittent expirations by regulating screws *G* (Fig. 1) and thus relieve considerable danger of excessive lung pressure. The expirations from the bellows reservoir can be maintained to flow with practically very little, if any, variations. The outfit is portable and can be kept connected. The face piece or pharyngeal tube can be connected at a short distance from the valve and thus eliminate dead space. The outfit can be worked either by foot or by one hand leaving the other hand free to look after the face mask or pharyngeal tube. The outfit should, however, rest on either a board or solid ground to insure uniform expirations as a sandy or soft ground may cause variation.

Since we do not ordinarily utilize our lungs to full capacity, I would here suggest setting a standard for the outfit. For example, record the average amount of air expired at each expiration from a number of adults. Sum up this total, and find an average lung capacity. Regulate the artificial respiration outfit accordingly for general use in emergency cases. There may be marked differences between male and female adults, but in such cases it might be advisable to have two or more such outfits so regulated. The outfit should be worked to correspond with normal breathing. Before applying artificial respiration see that the mouth is free of any foreign body, keep the tongue pulled forward, and see that the plunger in the valve reacts normally. While this outfit should not interfere with training along the Shäfer prone method, still the outfit is perhaps as safe as can be trusted in the hands of the layman.

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THE USE OF FLOCCULE-FORMATION REACTIONS TO CORROBORATE THE WASSERMANN TEST

By Ross J. MacCann, New York City

AMONG the diagnostic methods that are used for the detection of syphilis, the original Wassermann technic with some of its varied modifications, is the one that is mostly used in commercial laboratories. Many of these laboratories use two antigens, cholesterinized and noncholesterinized antigens, or an alcoholic extract of syphilitic liver; while a few use a third antigen, Noguchi's acetone-insoluble lipoid extract. Some laboratories use the Hecht-Weinberg, one of Kolmer's modifications, or the Hecht-Gradwohl method in conjunction with the regular Wassermann, so that anticomplementary findings may be reduced to a minimum.

The use of more than two antigens lengthens and complicates the tests; in the Hecht-Weinberg modification the serum should be used as soon as possible after the specimen is taken, utilizing as it does the complement and amboceptor in the patient's serum, which is perfectly feasible where Wassermanns are being done daily, but not where they are being done once or twice a week; while the Hecht-Gradwohl modification is inclined to be rather cumbersome, especially where many tests are to be made in a day; and in Kolmer's methods, two of them are almost similar to the Wassermann, while the other two consume a great deal of time and much material. All these modifications are excellent as corroborative reactions with the regular Wassermann, but where the time is limited, a shorter and yet reliable method would be more advantageous, and helpful in doubtful cases.

These doubtful or anticomplementary findings would not be commented on to any great degree, in hospitals, clinics, etc.; in a commercial laboratory they are a source of friction between laboratory and physician, and looked upon as a breach of contract, by the patient involved. He has paid his fee and naturally looks forward to a positive or negative report; when they receive a report with the explanation that their blood differs somewhat from others, and that the result is a doubtful one, it is a difficult task dispelling the patient's idea that it was due to carelessness, and not to the anticomplementary properties of his serum. Physicians also look to the laboratory for conclusive results on which to base their diagnosis, and combining the fact that they have recommended this particular laboratory, with their sincere wish of keeping the good-will and confidence of the patient, they are apt to feel a decided lack of faith in the skill of the serologist, and it is this lack of faith that we wish to avoid, being at the same time sincere in our dealings with both the physician and the patient.

With the thought that it might be possible to use one of these reactions outlined in the following pages, as a corroborative test with our regular Wassermann, and also that the interest of those engaged in commercial laboratories would be aroused, and that they would be stimulated into publishing their

research work, causing a reciprocity of ideas between those so engaged, I submit this article for publication.

In many diseases, and particularly syphilis, the serum of a patient thus afflicted, when mixed with colloidal solutions of lecithin or sodium glycocholate, forms a flocculent precipitate which may be seen macroscopically. Sodium taurocholate, taurin solution and distilled water, was used by Wieder and L'Engle, while other authors have used different solutions of hydrophilic colloids with varying results. The methods mentioned in the following pages were selected, because of their simple technic, and that workers have placed them at the head of the list for researching investigation.

The first method investigated was that of Porges and Meier, who use a 1 per cent lecithin solution in normal saline, and the serum diluted 1:5 with salt solution. One c.c. of the diluted serum was mixed with 0.2 c.c. of the lecithin, incubated at 37° for one hour, and left overnight at room temperature, results being read off the following morning. Nineteen serums, eight positives and eleven negatives were used in this test, and also in the fourth method; a smaller number being used in the second and third methods. Where inactivated serum was advocated by the author, we also used activated serum, the results obtained being nearly similar. The specificity of this method is low, approximately 45 per cent of the positive serums gave negative results, and 20 per cent of the negative serums gave positive results.

The second method was that of Elias, Neubauer, Porges and Salomon. One per cent of freshly made sodium glycocholate in distilled water is used in this test. Serums must be clear and contain very little hemoglobin. Two-tenths c.c. of the serum, activated and inactivated, is mixed with 0.2 c.c. of the solution and left from 16 to 20 hours at room temperature. The results obtained were slightly better and more accurate than the first method, but the advantages of this method are greatly lessened by the fact that only clear serums can be used in the tests.

The third method tested was that of Klausner, who employs distilled water, using serum undiluted and diluted 1 to 5 with distilled water. Two-tenths c.c. of each of the serums are mixed with 0.7 c.c. of distilled water, well shaken, and kept at room temperature for 15 hours, and readings then made. Results obtained were confusing and nonspecific.

The fourth method used was that of Herman and Perutz. They employ two solutions, the first being 2 per cent sodium glycocholate in 95 per cent alcohol, plus 0.4 gram of cholesterin; and the second solution is 2 per cent sodium glycocholate in distilled water. The first solution is diluted 1:20 with distilled water before using. In the test proper one part of (a) diluted, one part of (b), and two parts of serum are mixed, shaken gently, and let stand for 18 to 24 hours at room temperature. Results obtained were distinctly better and more accurate than in any of the other methods tested, but were only partially specific. Approximately 70-75 per cent of the positives gave positive results, while two of the eleven negative serums gave distinctly positive results, and one was extremely doubtful, due to a heavy clouding. Some earlier workers found this test equally as specific as the Wassermann in syphilitic cases; however, later observers fail

to confirm these earlier researches. Olitsky and Olmstead made a detailed study of this reaction in syphilitic and nonsyphilitic serums, and found it to be 61 per cent specific in 95 syphilitics and 80 per cent specific in 80 nonsyphilitics. Summarizing our observations on the results obtained in the tests of the above methods, it is quite obvious that, possibly with the exception of the Herman and Perutz method, these methods can not be used with any great degree of certainty to corroborate the Wassermann test, and especially so in those cases where the Wassermann gives a doubtful or anticomplementary result.

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EDITORIALS

Pathology of the Pneumonia in the United States Army Camps During the Winter of 1917-18

THE Rockefeller Institute for Medical Research has issued a monograph by Professor William G. MacCallum on the above-named subject. There is given a short historical survey of epidemics of pneumonia. In the sixteenth century such epidemics were well known in Italy. In 1535 one such epidemic apparently prevailed over the greater part of the Peninsula. The attack began with a chill, pain in the head and chest, and a cough at first dry but later attended by expectoration. Often the patient became delirious and later fell into a stupor. Death usually occurred on the sixth or seventh day, and the prognosis was good beyond this time. Pleural effusions were found and the lungs are stated to have been indurated and turbid, with frequent abscesses. Similar epidemics were reported in the seventeenth century. Several authors of that time reported the finding of serous and blood-stained effusions in the pleura and pericardium. For the most part, the lungs were consolidated, but occasionally rendered diffluent by suppuration. According to Hirsch so-called typhoid pneumonic epidemics were observed in England, Spain, Italy, Switzerland, France, and North America in

the eighteenth century. The type of the disease observed at that time was said to be highly malignant and the lungs were often found to contain much purulent material. In 1790 Desauvages and others described such disease among soldiers in France. They made postmortem examinations and found suppurative processes in the lungs with effusion of pus or gelatinous serum in the chest and sometimes in the pericardium. Similar epidemics were described by Noah Webster, the lexicographer, as occurring in Connecticut in 1712, 1719, 1760 and 1795. In 1812 there was a great epidemic which apparently started in Canada, spread through the northern part of the United States, and finally reached the South. There is a book by James Mann, hospital surgeon of the army, published in 1816 which gives a good description of the condition including a few postmortem observations. From these it is learned that the soldiers died with extensive pleural effusion sometimes of thick pus, as in the case of one man whose pleura was drained by an incision between the ribs, and sometimes of a thick yellowish whey-colored fluid, while a membrane of coagulated lymph lined the cavity of the thorax. Sometimes the lungs had a dark purple appearance and incision accompanied by compression forced out pus from the air cells. In other cases the lungs were contracted, compact, tough, and almost destitute of air cells. In some instances the lungs appeared like the liver, tender, easily lacerated with the fingers, and entirely destitute of the spongy texture peculiar to healthy lungs.

Even at that early date, measles as a predisposing cause of this form of pneumonia was recognized. McReynolds and Hudson described epidemic pneumonia among troops on the Niagara front. This epidemic prevailed among the soldiers in western New York in December, 1812, and January, 1813. From the soldiers and their camps it spread through New York and over the greater part of New England. The authors of that time did not describe minutely the pulmonary changes, but it is evident from their descriptions that this disease was not definite lobar pneumonia, but probably a form of bronchopneumonia with extensive pleural exudate. From 1815 to 1862 there were occasional epidemics.

Little information appears to be available regarding the prevalence of this disease among soldiers during the Civil War. Woodward gives statistical information showing that measles was prevalent, that pneumonia followed it, and that the mortality was considerable, but these conditions were overshadowed by the greater prevalence of typhoid fever and dysentery. Of the cases of bronchopneumonia following measles during the Civil War the lungs of three have been preserved in the Army Medical Museum and McCallum makes the following statement concerning his examination of one of these specimens:

"The history in Case 50 states that Private J. B. Talbot, age 23, was admitted February 13, 1864, with pleuropneumonia following measles and died February 29. Postmortem examination showed that the lower lobe of the right lung was hepatized, red, and presented on section a number of small superficial abscesses. The pleura was thickened. The lung is fibrinous, exudated, and most of it is spongy in texture, but it contains some distinct, firm nodules which are branched at times."

McCallum found that sections of this lung no longer stain well, but the outlines of cells may be discerned. There is in the section a patch of consolida-

tion. There are central bronchioles which contain exudate and have lost their epithelium. The walls are thick and infiltrated with mononuclear cells and are penetrated by many distended blood vessels. The adjacent alveolar walls are infiltrated and contain dense plugs of fibrin with desquamated epithelium. The larger area of consolidation shows several bronchi with the same change. The walls of a rather large one are especially infiltrated. More peripheral alveoli have dense contents of fibrin and epithelium. In the more central part of the patch the tissue is disintegrated and full of small broken cells, possibly leucocytes. There is a mass of granular material at one spot resembling bacteria. With proper stain, McCallum was able to demonstrate streptococci in the midst of the necrotic area. No other bacteria could be seen. There is no doubt of the existence and rather wide prevalence of streptococcal pneumonia among Northern Soldiers during the Civil War. Since that time other epidemics of pneumonia have been described, but it is difficult from the clinical description to determine the nature of the disease.

This form of bronchopneumonia was most carefully and skilfully investigated by Delafield. His understanding of the contrast between this type of pulmonary affection and the sort of exudative process which follows the aspiration of infected materials into the bronchi, or the other examples of terminal patchy pneumonia characterized by the filling of the alveoli which are connected with the infected bronchioles with an exudate of polymorphonuclear leucocytes, is satisfactory and his descriptions form a model of conciseness.

During the present war epidemic pneumonia has been carefully studied by many English physicians. They describe a purulent bronchitis which is fatal and from which they isolated the influenza bacillus in the sputum in most cases. However, they found other organisms including the pneumococcus, streptococcus, and staphylococcus.

Coming to his own work McCallum thinks that emphasis should be laid upon the importance of measles in the inception of this epidemic. It is well known that measles prevailed during the winter of 1917-18 most largely in camps filled by southern and rural troops, and it was in these camps that pneumonia most frequently followed measles. It should not be understood that bronchopneumonia did not occur except among those who had recently had measles. It did occur among both the measles and the nonmeasles group, but it was more common and much more deadly among the measles group. McCallum is of the opinion that soldiers who had recently had measles and therefore were in a condition of reduced resistance fell the first victims to the streptococcus. This organism having grown lusty and increased in virulence, found itself able to overcome the resistance of the most virile and was no longer compelled to await the debilitating effects of measles. We quote the following:

"The influenza bacillus was frequently in the sputum and occasionally in the lungs and pleural cavity. It was always associated with the streptococcus and it is difficult to assign it a predominant part in the causation of the pneumonia. In general, the pneumococcus of whatever type produced lobar pneumonia and the streptococcus either what we shall describe as interstitial bronchopneumonia, or another lesion to which for convenience we assign the name lob-

ular pneumonia. The exact biological nature of this streptococcus and its identity in different camps are still subjects which are actively discussed. It seems to be the same wherever it has been found, but it will require time to determine whether there are several strains at work. Indeed from many camps there come reports of numerous cases due to a nonhemolytic streptococcus. All these important points must be determined by further study which must also decide the significance of the influenza bacillus, staphylococcus, and other organisms in the production of the disease. Our own experience has led us to believe that a fairly constant hemolytic streptococcus is the important factor."

McCallum's studies were carried on principally at Fort Sam Houston, Texas, and at Camp Dodge, Iowa. Details are given concerning 44 cases studied in Texas and 40 in Iowa. The monograph contains well executed plates giving visual representation of the findings. Lobar pneumonia caused by the several types of pneumococcus was found, but the number of cases seems not especially different from what ordinarily occurs during corresponding months of the year. In some cases lobar pneumonia was combined with streptococcal pneumonia; in others the findings were in no way dissimilar to those usually observed in straight pneumococcal infections. The streptococcal infection seems to occur by way of the upper respiratory tract and the illness begins with a sore throat, cough, and fever. Physical signs in the lungs are indefinite until evidence of accumulation of fluid in the chest appears. Dyspnea of extreme type and especially during inspiration is characteristic and is indicated by a marked cyanosis. Most patients are alert, apprehensive, and sleepless, and there is often delirium. The first type of pulmonary lesion described is designated as interstitial bronchopneumonia. It is the result of infection of the bronchioles with hemolytic streptococci leading to marked changes in the bronchial walls and adjacent pulmonary tissue. The most striking accompaniment of this is collapse of the lung, affecting those portions formerly supplied with air by the obstructed bronchi, together with the formation of nodules of consolidation about the terminal portions of the bronchi. At the same time there is extreme engorgement of the blood vessels and hemorrhage into the tissue about the nodules of consolidation. The walls of the bronchi become densely infiltrated with mononuclear cells. Extreme hyperemia and the new formation of blood vessels and of connective tissue add greatly to the thickening and deformity of the walls. In some cases the whole lining of the bronchi becomes necrotic and presents the appearance of a diphtheritic pseudomembrane. Coincident with the changes in the bronchial walls are similar alterations in the walls of the adjacent alveoli. The alveolar capillaries are distended with blood, the epithelium is proliferated rapidly and desquamated into the alveolar cavity. These cavities are found to be filled with blood, fibrin, and desquamated epithelial cells. Those more distant contain smaller numbers of these cells and are filled with a thick viscid fluid. This gelatinous edema gives a semblance of confluence between the areas of consolidation before it is really completed. There are many cases in which the changes are restricted to the neighborhood of the bronchioles and separated from each other by wide areas of air-containing tissue. Streptococci are found in masses in the lumen of each bronchus or bronchiole mingled with the leucocytes of the

exudate, but in most instances they are not found abundantly in the substance of the tissue or in the alveolar contents.

The lymphatics which run from the pleural network by way of the interlobular septa, bronchial walls, and blood vessels to the nodes at the hilum of the lung quickly become a channel for the transport of these bacteria. Great numbers of bacteria are found in these canals and in the sinuses of the lymph nodes at the hilum where they appear to be detained. They cause thrombosis of the lymph channels which become distended to an enormous size and appear to the unaided eye as most conspicuous, beaded, white strands on the cut surface of the lung extending to connect with the pleural network, which may be in places similarly injected and distended with a white, infected, semipurulent thrombus. It is thought that bacteria extend by growth along these obstructed channels in both directions, and thus passing from the lung to the pleura, infect the walls of the pleural cavity and set up intense inflammation resulting in the formation of fluid exudate.

From the beginning of the infection of the pleura the effusion of exudate becomes a dominant feature both in clinical signs and anatomical changes. It proceeds with great rapidity and compresses the lung to such a degree as to complete the atelectasis. When the exudate accumulates in large quantities, such as two or more liters, the lung becomes an airless, pasty, blue clump of tissue which is plastic against the pericardium or back against the side of the vertebral column. Later the pleural exudate becomes more purulent, having begun as a thin, greenish, turbid fluid filled with streptococci, disintegrated leucocytes, and shreds of fibrin.

Rapid organization of the inflammatory exudate is everywhere in evidence. This affects the alveolar and bronchial contents which are replaced in part by connective tissue resulting in interstitial new growth which thickens the alveolar walls, the bronchial walls, the adventitia or blood vessels, and the interlobular septa. The thrombosed lymphatics become organized and occluded permanently by fibrous tissue so that new ones must eventually be formed, while absorption in the meantime is greatly hampered. Most striking is the rapid organization of the layer of fibria which covers the pleura. This results in the formation of thick vascular granulation tissue on the pleural surface, adhesions between contiguous surfaces are rendered permanent, and in the later stages incapsulated pockets of intrapleural origin filled with pus are not infrequently formed and offer difficulties to the surgeon.

Less frequently large portions of the lung become necrotic. Such material is loaded with streptococci and is often discharged through the bronchus, leaving a cavity. When such a cavity communicates with the pleura, pneumothorax may result, or if the chest is already open it appears as a bronchopleural fistula. Such a disease of the lung betrays its tendency to heal. Everything except perhaps the bronchial exudate, the pleural exudate, and the intrapulmonary necroses or abscesses partakes of the nature of a barricading process. All changes tend to limit the advance of the streptococci and to this end the tissue is indurated. The alveolar exudate with its fibrin later replaced by connective tissue, the thrombosis of the lymphatics, the thickening and granulation tissue formation in the

bronchial walls, interlobular septa, and pleura, and the wide-spread hyperplasia of lymphoid tissue throughout the lung, are all evidence of a considerable power of resistance which permits the body time for defense. The infection is fairly well localized in the respiratory tract and there is no septicemia until perhaps the last few hours of life. Other organs suffer but little.

The type designated as lobular pneumonia is shown in cases in which the streptococci invade in the same way. One does not know how to distinguish the symptoms and yet at autopsy although sometimes even the lungs may look much the same at a casual glance, they are really different. There are no firm peribronchial nodules. There are patches of consolidation in which the alveoli are filled with blood, leucocytes, and enormous quantities of streptococci. There are no interstitial changes and no signs of resistance. Widespread necrosis occurs with final destruction of areas of lung tissue. Hemorrhage about these areas is usual and there is often pleural effusion without any organization of the exudate. There are cases in which this lobular pneumonia occurs in pure form, but there are many more in which it is found side by side with the interstitial bronchopneumonia. There are different expressions of reaction to the same infection, but in these the reaction is feeble. There is nothing new in the forms of pneumonia in this epidemic. They have existed always and, historically, can be traced back at least to the sixteenth century. More scientific descriptions date from 1812, and perfectly clear ones from Delafield in 1884.

—*V. C. V.*

*Shock**

ONE of the most striking developments of modern pathology—not to say physiology—is that which relegates the nervous system to a distinctly subordinate place. This development has resulted in placing chemical and physicochemical action in a commanding position, and in assigning to the nervous system a sort of controlling function. In the absence of a nervous system pathologic changes develop, as they do in the presence, but the rate of development is abnormally slow. Evidently the nervous system influences the speed of reactions. Nowhere is this more striking than in shock.

It has not been so long since shock was referred to nervous impulse alone. Extreme nervous irritations acting, over a sufficient period of time, upon the vasomotor centers lead to fatigue of those centers, with the result that the vessels—chiefly the arterioles—lost their tone and power of constriction, and that the blood pressure fell, and was recovered only with the greatest difficulty. Later observations showed that the reverse was true; i. e., that the vasomotor mechanism remained intact; that instead of a dilatation of the arterioles, they were constricted. Despite this arterial state the blood pressure fell, and remained low during the progress of the state of shock.

*Tissue Toxemia as a Factor in Shock. Reports of the Special Investigation Committee on Surgical Shock and Allied Conditions. Special Rept. No. 28. Medical Research Committee. Oxford University Press, March 14, 1919.

Later also it was found that the low blood pressure was the result of lack of blood volume. When hemorrhage had occurred this was readily understood; when it had not occurred it was explained with difficulty. Blood examinations in the latter type of cases showed that the blood was concentrated; i.e, that the corpuscles were increased in unit volumes, and that the plasma was decreased. Evidently therefore the loss of blood volume was due to loss of fluid from the blood, but not to loss of the formed elements, and, since hemorrhage had not occurred, the fluid must have passed into the tissues. So the problem was shifted from the vessels to the tissues. Why did the fluid of the blood pass outward? Why should the fluids be attracted to the tissues? It is one of the great contributions of Y. Henderson, that he focused attention upon this aspect of the problem. Henderson believed that an early symptom of shock was hyperpnea, caused by the sensory impulses originating in a damaged area of the body, and that this resulted in a washing out of CO_2 from the lungs and vascular system. So a condition of acapnia was produced which acted to reduce the diastolic pressure in the heart by reducing pressure in the veins. At the same time the ratio of CO_2 in the blood to CO_2 in the tissues fell and this led to a flow of water from the blood to the more acid tissues. In other words a condition of more or less generalized tissue acidosis occurred which led to edema of the various organs, and coincident concentration of the blood.

At the beginning of the war these two conceptions of shock were held; the one which laid the failure of the circulation at the door of vasomotor fatigue—the result of overstimulation of the centers—and the other which held that the vasomotor centers were abnormally active, and that the main factor was a condition of tissue acidosis which resulted in concentration of the blood to such an extent that the heart no longer was supplied with enough blood to pump, even when the arterioles were in a state of maximal constriction. The war experiences have tended to discredit the former theory and to support the latter.

The observations at the front in Casualty Clearing Stations and First Aid Stations have been made the basis of experimentation. One prime conclusion has been reached; i.e., that muscle injury can produce a state of shock, and that absorption of toxins or similar substances can do the same. These conclusions rest upon the following clinical evidence: (1) The experience that, putting aside gross injuries, the shock from which the abdominally wounded man suffers, depends more on the loss of blood, or on peritonitis and sepsis, than on the extent of the lesion. Many men thought by the surgeon to have died of shock, have been proved by postmortem examination to have died of acute sepsis or gas gangrene. (2) The striking change for the better that follows excision of muscles infected by anaerobic bacilli. (3) The well-known association between shock and small multiple or single large muscle wounds. (4) The shocking nature of operations involving large muscle masses (amputation at the hip). This clinical evidence may be summarized by saying that shock (secondary shock) is the result of an intoxication. What are the toxins?

In certain cases it may be that bacteria are the active causes of shock; that they produce substances which bring about the whole sequence of events. Such a state of affairs we might call bacteriotoxemic shock. In certain other cases in which the bacteria are not present, there must be other substances, not of bac-

terial origin, but of tissue origin which cause the typical sequence of events. This we might call histo-toxemic shock. Recent experimental work has concerned itself to a large extent with the latter, and with such evidently successful results that we may well wonder whether the former is not the result of bacterial action upon the tissues, setting free toxic substances,—in other words, whether after all the condition of shock is not always a tissue affair, hastened or modified in certain cases, by bacteria.

At the front, shock was associated with other conditions than muscle damage and infection; i.e., hemorrhage, pain, cold, mental distress, and rough handling. Elimination of cold and rough handling were most effective in treatment. Warmth tended to improve the circulation; gentle treatment tended to reduce muscle damage and pain. Administration of morphine in small doses was valuable because it relieved pain, and tended to quiet. Large doses of this drug were dangerous, probably because they tended to decrease oxidations in the body. Administrations of fluid were of very real value, because of the replenishment of the water in the blood vessels. Gum (colloidal) solutions given intravenously were valuable because the gum tended to retain the absorbed water and keep it in the vessels, and so reestablish the blood volume and pressure.

Wallace says that acidosis can be neglected as a cause of shock, but it would seem that the whole sequence of the events, and the methods of treatment point to the fact that tissue acidosis is the essential condition of the complex, and that to it are due the various clinical manifestations. Whether hyperpnea with subsequent acapnia, or a primary toxemia due to tissue destruction, or loss of blood alone forms the starting point of the complex, any one or all combined tend to produce a chemical state in the organs and tissues of the body which may logically be called acidosis, which is the condition upon which depends withdrawal from the blood vessels. The effects of anesthetics point to the same conclusion, for chloroform is the most dangerous one, ether follows it, and gas-oxygen is safest.

Cannon, Bayliss and others have subjected animals to experiments to determine the actual condition supervening upon muscle damage. They found that if they ruptured and severely bruised muscles, without breaking the skin, the muscles underwent considerable swelling and some extravasation of blood though not sufficient to produce symptoms of hemorrhage. During the process of traumatization the blood pressure fell and was followed sometimes by a temporary rise, after which a secondary fall occurred. The promptness of the primary fall suggested that it was reflex, but it occurred after the cord had been cut. It failed to appear if the aorta was closed above the iliacs during the traumatization although the nerve conduction would not be impaired during this short anemia. There was no change in the alkaline reserve during the period of the primary fall. The observations indicate that the sharp fall is not due to any general effect of the trauma on the circulation brought about through nervous agencies or liberated acid. It may be due to a combination of dilatation of blood vessels in the injured area together with some extravasation of blood, with the rapid setting free of a chemical substance acting as a powerful depressant on the blood pressure. The secondary fall may be explained by the continued absorption of the depressant substance and by the establishment of a vicious circle in consequence

of the low blood pressure. This is associated with a steady fall in the bicarbonate reserve of the blood. A remarkable effect on the respiration is usually to be seen. The rate increases greatly and the depth is shallow. These experimental results are strikingly similar to cases of shell traumata seen in men wounded in battle. In all such cases the shock was accompanied by acidosis.

Erlanger and his associates have observed that temporary exclusion of the circulation from any considerable part of the body results in shock. Cannon and Bayliss have made similar observations and they point out that muscles produce certain products, especially when the oxygen supply is diminished or cut off, which, when set free in the circulation, lower the blood pressure. At the same time the alkaline reserve falls. They also have shown that massage of damaged muscles, results in a further fall of blood pressure.

Bayliss says it appears that the conclusion must be drawn that the toxic products can be removed or destroyed as quickly as they pass into the blood current if the volume of the blood is kept sufficiently large to insure a good circulation and supply of oxygen to the tissues. Whether the toxic products are oxidized, as lactic acid is, or rendered harmless by passing through the liver, is not known as yet. We know that histamine disappears very rapidly if the circulation is effective.

A large amount of recent experimental work has concerned itself with this substance histamine which is a protein split-product, a derivative of the amino acid histidine. Injection of this substance into the veins of experimental animals produces a condition that is typically shock. The blood pressure falls and the respirations become feeble. At first sight one receives the impression that the heartbeat has become feeble almost to extinction; but if the chest is opened, the heart is seen to be beating strongly and regularly, but its chambers contain remarkably little blood. The veins and arteries seem to contain but little blood and are constricted. The liver is pale and certainly not distended with blood, and the same is true of the spleen. The blood itself is markedly concentrated. It is an interesting fact in this conclusion that animals can tolerate only exceedingly small doses of histamine if this operation is combined with ether anesthesia.

The whole trend of the work up to the present time seems to indicate in a very definite way that secondary shock is the expression of a toxemia which is frequently the result of tissue damage. Such damage sets free, of itself, or with the assistance of bacteria, substances like histamine which are products of incomplete protein splitting, which, in the presence of sufficient oxygen supplies, are readily removed. Any circumstances that decrease oxidation accumulate the shock.

—*P. G. W.*

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